(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2003 (26.06.2003)

PCT

(10) International Publication Number
WO 03/051877 A1

(51) International Patent Classification[7]: C07D 471/04, A61K 31/437, A61P 35/00

(21) International Application Number: PCT/US02/40328

(22) International Filing Date:
18 December 2002 (18.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/341,367	18 December 2001 (18.12.2001)	US
60/342,310	19 December 2001 (19.12.2001)	US

(71) Applicants *(for all designated States except US)*: **BAYER CORPORATION** [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US). **BAYER AKTIENGESELLSCHAFT** [DE/DE]; D-51368 Leverkusen (DE).

(72) Inventor: **NIEWOEHNER, Ulrich** (deceased).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHANG, Chengzhi** [CA/US]; 193 Mulberry Lane, Orange, CT 06477 (US). **FAN, Dongping** [CN/US]; 114 Fitch Street, North Haven, CT 06473 (US). **WANG, Yamin** [CN/US]; 10 Russet Road, Sandy Hook, CT 06482 (US). **LI, Tindy** [US/US]; 102 Wharton Place, West Haven, CT 06516 (US). **BOYER, Stephen, J.** [US/US]; 233 Colony Street, Fairfield, CT 06430 (US). **BURKE, Jennifer** [US/US]; 216 Bishop Street, Apt. 309, New Haven, CT 06511 (US). **RAUDENBUSH, Brian, C.** [US/US]; 157 Leeder Hill Drive, #407, Hamden, CT 06518 (US). **WONG, Wai, C.** [US/US]; 314 Aspen Glen Drive, Hamden, CT 06518 (US). **YING, Shihong** [CN/US]; 280 Bittersweet Road, Orange, CT 06477 (US). **WANG, Ming** [US/US]; 32 Milford Hunt Lane, Milford, CT 06460 (US). **ZHAO, Qian** [CN/US]; 93 Hintz Drive, Wallingford, CT 06492 (US). **CARTER, Christopher, A.** [US/US]; 48 Blue Hills Drive, Guilford, CT 06437 (US). **BURKHARDT, Nils** [DE/DE]; Huegelstrasse 20, D-40589 Duesseldorf (DE). **PERNERSTORFER, Josef** [AT/DE]; Alsenstr. 19, D-42103 Wuppertal (DE). **NIEWOEHNER, Maria** [DE/DE]; Gartenstrasse 3, D-42929 Wermelskirchen (DE).

(74) Agents: **GREENMAN, Jeffrey, M.** et al.; Bayer Corporation, 400 Morgan Lane, West Haven, CT 06516 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 2-SUBSTITUTED PYRROLO[2.1-A]ISOQUINOLINES AGAINST CANCER

(57) Abstract: The present invention relates to 2-substituted pyrrolo[2.1-a]dihydroisoquinoline compounds which are inhibitors of phosphodiesterase 10a and can be used for com-batting cancer.

WO 03/051877 A1

2-SUBSTITUTED PYRROLO(2.1-A)ISOQUINOLINES AGAINST CANCER

BACKGROUND OF THE INVENTION

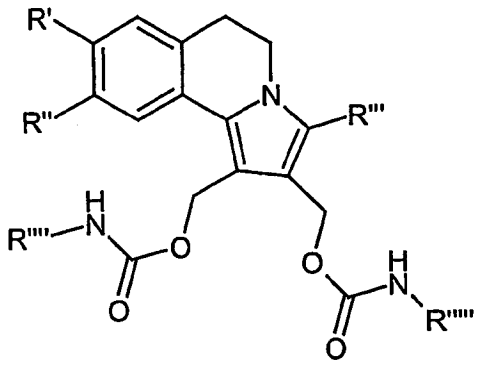
The present invention relates to 2-substituted pyrrolo[2.1-a]isoquinoline derivatives which are inhibitors of phosphodiesterase 10a, a process for preparing these compounds and a method of treating cancer by administering these compounds.

Cyclic AMP metabolism is regulated by the opposing activities of adenylyl cyclase, which generates cAMP in response to extracellular stimuli (e.g. engagement of G-protein coupled receptors by their cognate ligands), and 3',5'-cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze cAMP to 5'-AMP. Signal transduction via cAMP is associated with transcriptional events that can result in the inhibition of cellular proliferation (T.J. Shaw et al., Exp. Cell Res. 273, 95 (2002); T.W. Moody et al., Ann. N.Y. Acad. Sci. 921, 26 (2000); W.L. Lowe et al., Endocrinology 138, 2219 (1997); D.A. Albert, J. Clin. Invest. 95, 1490 (1995); M.I. Mednieks et al., FEBS Lett. 254, 83 (1989)). Indeed, elevation of intracellular cAMP concentration is growth inhibitory for several human tumor cell lines, including those derived from breast, lung and colorectal carcinomas (B. Wagner et al., Biochem. Pharmacol. 63, 659 (2002); S.B. Jakowlew et al., Peptides 21, 1831 (2000); I.S. Fentimen et al., Mol. Biol. Med. 2, 81 (1984); P. Cassoni et al., Int. J. Cancer 72, 340 (1997); S. Shafer et al., Biochem. Pharmacol. 56, 1229 (1998); N.M. Hoosein et al., Regul. Peptides 24, 15 (1989)). In several human breast carcinoma cell lines, increased cAMP production through stimulation of adenylate cyclase activity and/or reduction in cAMP catabolism through inhibition of phosphodiesterase activity has been shown to result in increased steady state levels of cAMP and growth inhibition (D. Melck et al., FEBS Letters 463, 235 (1999); N. Veber et al., Eur. J. Cancer 30A, 1352 (1994); J.A. Fontana et al., J. Natl. Cancer Inst. 78, 1107 (1987); T.A. Slotkin et al., Breast Cancer Res. and Treatment 60, 153 (2000)). In contrast to breast tumor cell lines, normal human mammary epithelial cells are stimulated to proliferate by elevation of intracellular cAMP (I.S. Fentimen et al., Mol. Biol. Med. 2, 81 (1984)). These observations suggest that elevation of intracellular cAMP may selectively inhibit breast tumor cell proliferation. Interestingly, it has been reported that neoplastic mammary tissues have higher levels of low-Km phosphodiesterase activity compared to normal breast tissue, suggesting that tumors may

gain a growth or survival advantage by keeping intracellular cAMP levels in check (A. Larks Singer et al., Cancer Res. 36, 60 (1976)).

The ICAST (Inhibitor of Cyclic AMP Signal Transduction) gene encodes a specific 3',5'-cyclic nucleotide phosphodiesterase. Compared to corresponding normal tissues, ICAST mRNA is overexpressed in breast carcinoma specimens, liver metastases of colorectal carcinoma and non-small cell lung carcinomas. The ICAST cDNA was also recently cloned by other groups and named PDE 10a (K. Fujishige et al., J. Biol. Chem. 274, 18 438 (1999); S.H. Soderling et al., Proc. Natl. Acad. Sci. USA 96, 7071 (1999); K. Loughney et al., Gene 234, 109 (1999)). Published expression data for ICAST mRNA show a very limited distribution across adult human tissues, with highest levels observed in the testis, caudate nucleus and putamen (K. Fujishige et al., 1999). Increased expression of ICAST mRNA in human tumor specimens indicates that ICAST may play an important role in tumor cell growth and/or survival under conditions of elevated cAMP generation. Selective inhibition of ICAST activity in tumor cells should lead to increased cAMP concentrations and growth inhibition. The expression profile of ICAST and the published reports indicating that breast, lung and colon carcinomas are particularly sensitive to elevation of intracellular cAMP indicate that ICAST may play critical roles specifically in those tumor types. In addition to elevation of cAMP, inhibition of ICAST activity should also decrease the intracellular concentration of 5-AMP, which could limit purine pools and DNA synthesis in rapidly dividing tumor cells.

Pyrrolo[2.1-a]isoquinoline derivatives of formula (A) are described in J. Med. Chem. 27, 1321 (1984) and in J. Med. Chem. 31, 2097 (1988):

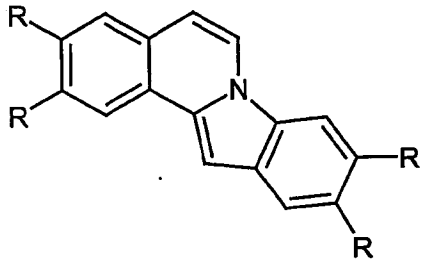


(A)

R' = H, OMe, Cl
R'' = H, Cl
R''' = H, Me
R'''', R''''' = Me, Et, i-Pr, C_6H_{11}

These compounds are described as having antineoplastic activity, which however is stated to be due to the carbamate moieties being electrophilic centers enabling the compounds (A) to react via an alkyl-oxygen cleavage mechanism. It is not mentioned that these compounds have any PDE 10a inhibitory activity.

Tetracyclic compounds of formula (B) containing a pyrrolo[2.1-a]isoquinoline moiety are described in Arch. Pharm. 321, 481 (1988):

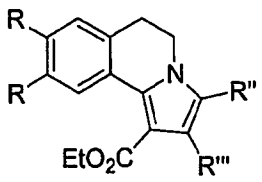


(B)

R = H, OMe

The compounds (B) are described as having anti-tumor activity due to their ability to intercalate into DNA. It is not mentioned that they have any PDE 10a inhibitory activity.

The synthesis of pyrrolo[2.1-a]isoquinoline derivatives of formula (C) is described in H. Meyer, Liebigs Ann. Chem. 9, 1534-1544 (1981):

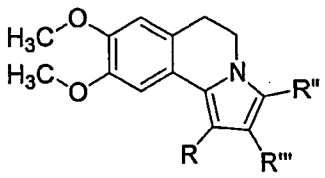


(C)

R = H, OCH_3
R" = CH_3, C_6H_5
R''' = C_6H_5

These compounds are not described as having any biological activity, and it is not mentioned that they have any PDE 10a inhibitor activity.

Compounds of the formula (D) are described in GB 1 153 670 A:

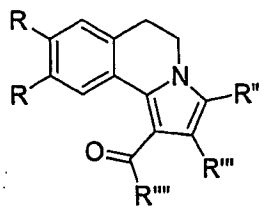


(D)

R = H, CO_2H, CO_2R''''
R" = H, CO_2H, CO_2R''''
R''' = C_6H_5, CH_3, CO_2R''''

These compounds are described as having hypotensive, sympathicolytic and psychotropic properties, but it is not mentioned that they have any PDE 10a inhibitory activity.

The synthesis of compounds of the formula (E) is described in US Patent 4,694,085:

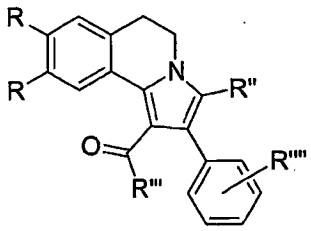


(E)

R = H, CH_3, OCH_3
R" = H, CH_3
R"' = C_6H_5, CH_3, CO_2R''''
R"" = H, CH_3

It is not mentioned that these compounds have any PDE 10a inhibitory activity.

Derivatives of the formula (F) are described in WO 98/55118:



(F)

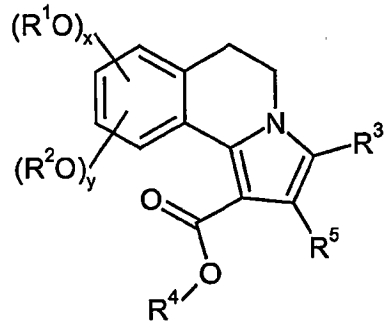
R = H, Cl, OCH_3
R" = CH_3
R"' = OR'''', CH_3, NH_2
R"" = H, CH_3, OR''''

These compounds are described as useful for the treatment of diseases such as psoriasis. However, the compounds disclosed in WO 98/55118 are described as having virtually no cytotoxic activity; it is not mentioned that they have any PDE 10a inhibitor activity.

BRIEF SUMMARY OF THE INVENTION

Surprisingly, it has been found that the 2-substituted pyrrolo[2.1-a]isoquinoline derivatives of the present invention inhibit PDE 10a and exhibit an antiproliferative activity.

The present invention relates to a compound of the formula



(I)

wherein

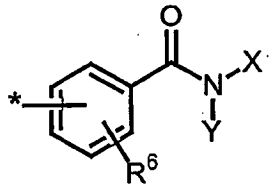
x and y independently from each other denote zero or 1;

R^1 and R^2 independently from each other denote hydrogen, C_{1-4}-alkyl or trifluoromethyl or

R^1 and R^2 together form a C_{1-4}-alkylene bridge;

R^3 and R^4 independently from each other denote C_{1-6}-alkyl optionally further substituted with halogen up to perhalo;

R^5 denotes a radical of the formula



wherein

R^6 denotes C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, halogen, hydrogen, hydroxy or C_{1-6}-alkoxy;

X and Y independently from each other denote

i) hydrogen;

ii) C_{1-6}-alkoxy;

iii) C_{3-8}-cycloalkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, benzyloxy, C_{1-6}-trialkylsilyloxy, halogen and C_{1-6}-alkoxy;

iv) C_{5-8}-cycloalkyl fused to C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of hydoxyl, C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, C_{3-8}-cycloalkyl, halogen and C_{1-6}-alkoxy;

v) C_5-C_{10}-bridged bicycloalkyl;

vi) C_6-C_{10}-aryl optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkoxy, (C_{1-6}-alkyl)-carbonyl, (C_{1-6}-alkoxy)-carbonyl, trifluoromethyl, trifluoromethoxy and halogen;

vii) phenyl fused to a 5- to 7-membered saturated cycloalkyl, optionally containing up to two hetero atoms selected from the group consisting of O, N, and S;

viii) heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkoxy, phenyloxy, benzyloxy, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, halogen and benzyl;

ix) heteroaryl; or

x) C_{1-6}-alkyl, optionally having from 1 to 3 substituents selected from the group consisting of

a) halogen up to perhalo,

b) cyano,

c) $-OR^7$,

d) $-NR^7R^8$,

e) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, nitro, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, -OR^7, -NR^7R^8, (C_{1-6}-alkyl)-carbonyl, (C_{1-6}-alkoxy)-carbonyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, -$C(O)NR^7R^8$, cyano, -SR^7, and C_6-C_{10}-aryl,

f) phenyl fused to a 5- to 7-membered saturated cycloalkyl, optionally containing up to two hetero atoms selected from the group consisting of O, N, and S,

g) heteroaryl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-8}-cycloalkyl, hydroxy, C_{1-6}-alkoxy, benzyloxy, halogen and trifluoromethyl,

h) heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, halogen and benzyl, and

i) C_{3-8}-cycloalkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy and hydroxy;

wherein R^7 and R^8 independently from each other denote

1) hydrogen,

2) C_{1-6}-alkyl, optionally further substituted with 1 to 3 substituents selected from the group consisting of hydroxyl and halogen,

3) C_{3-8}-cycloalkyl,

4) benzyl,

5) C_6-C_{10}-aryl optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkoxy, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy and halogen, or

6) heteroaryl;

or

X and Y together with the nitrogen atom to which they are attached form heteroaryl or heterocyclyl, wherein said heteroaryl or heterocyclyl may optionally have from 1 to 3 substituents selected from the group consisting of

i) C_{3-8}-cycloalkyl;

ii) C_{1-6}-alkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{3-8}-cycloalkyl, hydroxy, C_{1-6}-alkoxy, halogen, phenylamino, morpholinyl, (C_{1-6}-alkyl)-aminocarbonyl, benzo[2,3]dioxolyl and C_6-C_{10}-aryl, wherein said aryl is optionally substituted with C_{1-6}-alkyl or C_{1-6}-alkoxy;

iii) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy and cyano,

iv) hydroxy;

v) C_{1-6}-alkoxy;

vi) C_{1-6}-dialkylamino;

vii) (C_{1-6}-alkoxy)-carbonyl;

viii) aminocarbonyl; and

ix) heteroaryl;

or

X and Y together with the nitrogen atom to which they are attached form heterocyclyl fused to C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkoxy and hydroxymethyl;

or

X denotes hydrogen and

Y denotes $-NR^9R^{10}$;

wherein R^9 and R^{10} independently from each other denote

1) hydrogen,

2) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkoxy, trifluoromethoxy and trifluoromethyl,

3) heterocyclyl,

4) C_{3-8}-cycloalkyl, or

5) C_{1-6}-alkyl;

or

R^9 and R^{10} together with the nitrogen atom to which they are attached form heterocyclyl or heteroaryl, wherein said heteroaryl or heterocyclyl may optionally have from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen and methoxymethyl;

and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

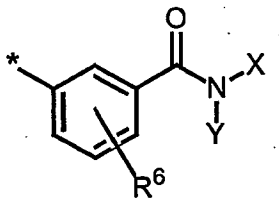
An alternative embodiment of the present invention relates to compounds of the formula (I), wherein

x and y independently from each other denote zero or 1;

R^1 and R^2 independently from each other denote hydrogen, C_{1-4}-alkyl or trifluoromethyl;

R^3 and R^4 independently from each other denote C_{1-6}-alkyl optionally further substituted with halogen up to perhalo;

R^5 denotes a radical of the formula



wherein

R^6 denotes halogen, hydrogen, hydroxy or C_{1-6}-alkoxy;

X and Y independently from each other denote

i) hydrogen;

ii) C_{1-6}-alkoxy;

iii) C_{3-8}-cycloalkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, benzyloxy and C_{1-6}-trialkylsilyloxy;

iv) C_{5-8}-cycloalkyl fused to C_6-C_{10}-aryl, optionally substituted with 1 to 3 hydoxyl;

v) C_5-C_{10} bridged bicycloalkyl;

vi) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy and (C_{1-6}-alkyl)-carbonyl;

vii) phenyl fused to a 5- to 7-membered saturated cycloalkyl, optionally containing up to two hetero atoms selected from the group consisting of O, N, and S;

viii) heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkoxy, phenyloxy, benzyloxy, and benzyl;

ix) heteroaryl; or

x) C_{1-6}-alkyl, optionally having from 1 to 3 substituents selected from the group consisting of

a) halogen up to perhalo,

b) cyano,

c) $-OR^7$,

d) $-NR^7R^8$,

e) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, nitro, hydroxy, C_{1-6}-alkyl, $-NR^7R^8$, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy and C_6-C_{10}-aryl,

f) phenyl fused to a 5- to 7-membered saturated cycloalkyl, optionally containing up to two hetero atoms selected from the group consisting of O, N, and S,

g) heteroaryl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, benzyloxy and trifluoromethyl,

h) heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl and benzyl, and

i) C_{3-8}-cycloalkyl, optionally further substituted with 1 to 3 substituents hydroxy;

wherein R^7 and R^8 independently from each other denote

1) hydrogen,

2) C_{1-6}-alkyl, optionally further substituted with 1 to 3 substituents hydroxyl,

3) benzyl,

4) C_6-C_{10}-aryl, optionally further substituted with 1 to 3 substituents C_{1-6}-alkoxy, or

5) heteroaryl;

or

X and Y together with the nitrogen atom to which they are attached form heteroaryl or heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of

i) C_{3-8}-cycloalkyl;

ii) C_{1-6}-alkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{3-8}-cycloalkyl, hydroxy, C_{1-6}-alkoxy, phenylamino, morpholinyl, (C_{1-6}-alkyl)-aminocarbonyl, benzo[2,3]dioxolyl and C_6-C_{10}-aryl, wherein said aryl is optionally substituted with C_{1-6}-alkyl or C_{1-6}-alkoxy;

iii) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkoxy, trifluoromethyl and cyano;

iv) hydroxy;

v) C_{1-6}-alkoxy;

vi) C_{1-6}-dialkylamino;

vii) (C_{1-6}-alkoxy)-carbonyl;

viii) aminocarbonyl; and

ix) heteroaryl;

or

X and Y together with the nitrogen atom to which they are attached form heterocyclyl fused to C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy and hydroxymethyl;

or

X denotes hydrogen and

Y denotes $-NR^9R^{10}$;

wherein R^9 and R^{10} independently from each other denote

1) hydrogen,
2) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkyl and trifluoromethyl,
3) heterocyclyl,
4) C_{3-8}-cycloalkyl, or
5) C_{1-6}-alkyl;

or

R^9 and R^{10} together with the nitrogen atom to which they are attached form heterocyclyl or heteroaryl, wherein said heterocyclyl or heteroaryl optionally have from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl and methoxymethyl;

and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

A further alternative embodiment of the present invention relates to a compound of the formula (I), wherein

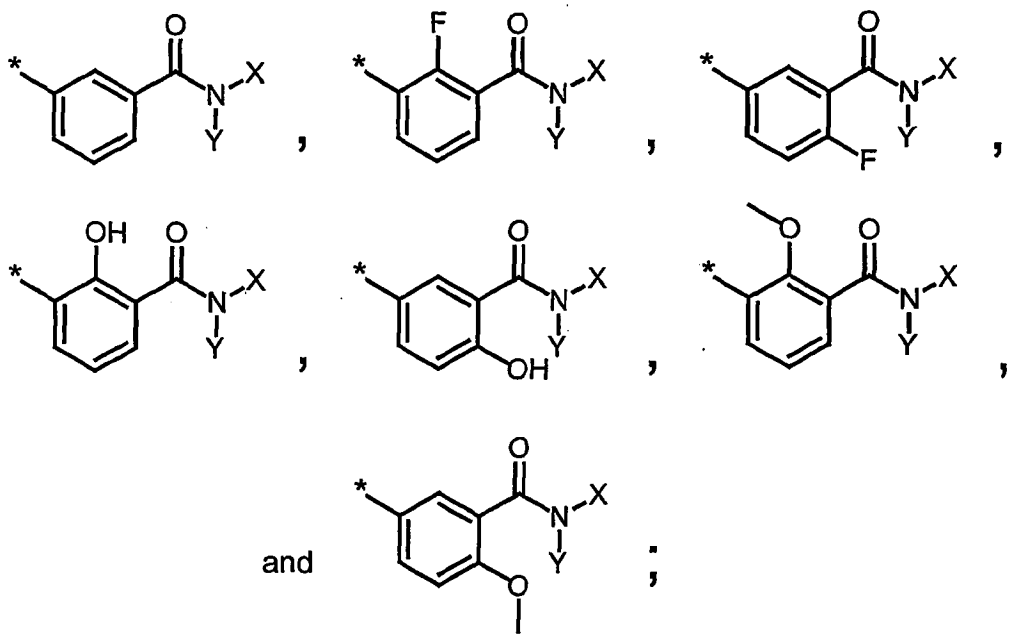
x and y each other denote 1

R^1 and R^2 independently from each other denote hydrogen or C_{1-4}-alkyl;

R^3 denotes C_{1-6}-alkyl or trifluoromethyl;

R^4 denotes C_{1-4}-alkyl;

R^5 denotes a radical of the formula selected from the group consisting of:



wherein

X and Y independently from each other denote

i) hydrogen;

ii) C_{1-6}-alkoxy;

iii) C_{3-8}-cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, said C_{3-8}-cycloalkyl optionally having from 1 to 2 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, benzyloxy and *tert*-butyldimethylsilyloxy;

iv) indanyl, 2-hydroxyindanyl, or 1,2,3,4-tetrahydronaphthalenyl;

v) [2.2.1]bicycloheptane;

vi) naphthyl, 4-methoxyphenyl, 3-(C_{1-6}-alkoxycarbonyl)phenyl or 2-methoxy-4-methylphenyl;

vii) benzo[2,3]dioxolyl;

viii) pyrrolidinyl, optionally having from 1 to 2 substituents selected from the group consisting of C_{1-6}-alkoxy, phenyloxy, benzyloxy and benzyl;

ix) thiazolyl, or pyridyl; or

x) C_{1-6}-alkyl, optionally having from 1 to 2 substituents selected from the group consisting of

a) halogen up to perhalo,

b) cyano,

c) hydroxy, C_{1-6}-alkoxy, benzyloxy, hydroxy-C_{2-6}-alkoxy, or methoxyphenoxy,

d) C_{1-6}-dialkylamino, di-(hydroxy-C_{1-6}-alkyl)-amino, pyridylamino, or anilino,

e) C_{6-10}-aryl selected from the group consisting of naphthyl and phenyl, said C_{6-10}-aryl optionally having from 1 to 2 substituents selected from the group consisting of fluoro, chloro, bromo, iodo, nitro, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, phenyl, amino and C_{1-6}-dialkylamino,

f) benzo[2,3]dioxolyl, or 2,3-dihydrobenzo[1,4]dioxinyl,

g) heterocyclyl selected from the group consisting of pyrazolyl, pyrazinyl, pyrrolyl, furyl, indolyl, thienyl, imidazoyl, and pyridyl, said heterocyclyl optionally having from 1 to 2 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, benzyloxy and trifluoromethyl,

h) morpholino, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, optionally further substituted with 1 to 2 substituents C_{1-6}-alkyl or benzyl, and

i) C_{3-8}-cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, said C_{3-8}-cycloalkyl optionally being further substituted with 1 to 2 substituents hydroxy;

or

X and Y together with the nitrogen atom to which they are attached form

i) morpholino, optionally further subsituted with 1 to 2 substituents C_{1-6}-alkyl;

ii) piperidinyl, optionally having from 1 to 2 substituents selected from the group consisting of hydroxyl, hydroxymethyl and C_{1-6}-alkyl;

iii) pyrrolidinyl, optionally having from 1 to 2 substituents selected from the group consisting of C_{1-6}-dialkylamino, pyridyl, carboxamido, C_{1-6}-alkoxy, phenylaminomethyl, methoxymethyl and methoxyphenyl; or

iv) piperazinyl, optionally having from 1 to 2 substituents selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, benzyl, morpholinoethyl, C_{1-6}-alkyl, (C_{1-6}-alkoxy)-carbonyl, (C_{1-6}-alkylaminocarbonyl)methyl, pyridyl, pyrazinyl, pyridylmethyl, benzo[2,3]dioxolyl and phenyl, wherein said phenyl is optionally substituted with 1 to 2 substituents selected from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, cyano and C_{1-6}-alkoxy;

or

X and Y together with the nitrogen atom to which they are attached form dimethoxytetrahydroisoquinolinyl, 2-methyl-6-fluorotetrahydroquinolinyl, indolinyl, isoindolinyl or 2-hydroxymethyltetrahydroisoquinolinyl;

or

X denotes hydrogen and

Y denotes

a) phenylamino, having from 1 to 2 substituents selected from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl and C_{1-6}-alkyl;

b) piperidinyl, optionally further substituted with 1 to 2 C_{1-6}-alkyl;

c) triazolyl;

d) pyrrolidinyl, optionally further substituted with 1 to 2 methoxymethyl;

e) morpholino;

f) imidazoyl;

g) C_{3-8}-cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

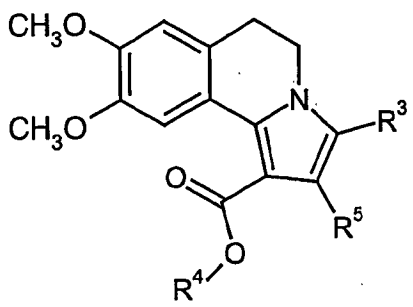
h) C_{1-6}-dialkylamino; or

i) azepanyl;

and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

A further alternative embodiment of the present invention relates to the compounds of the Examples 4, 6, 67, 77, 90, 93, 158, 170, 171, 227, 234, 244, 284, 295, 313, 376, 392 and 381.

A further alternative embodiment of the present invention relates to a compound of the formula (I'):

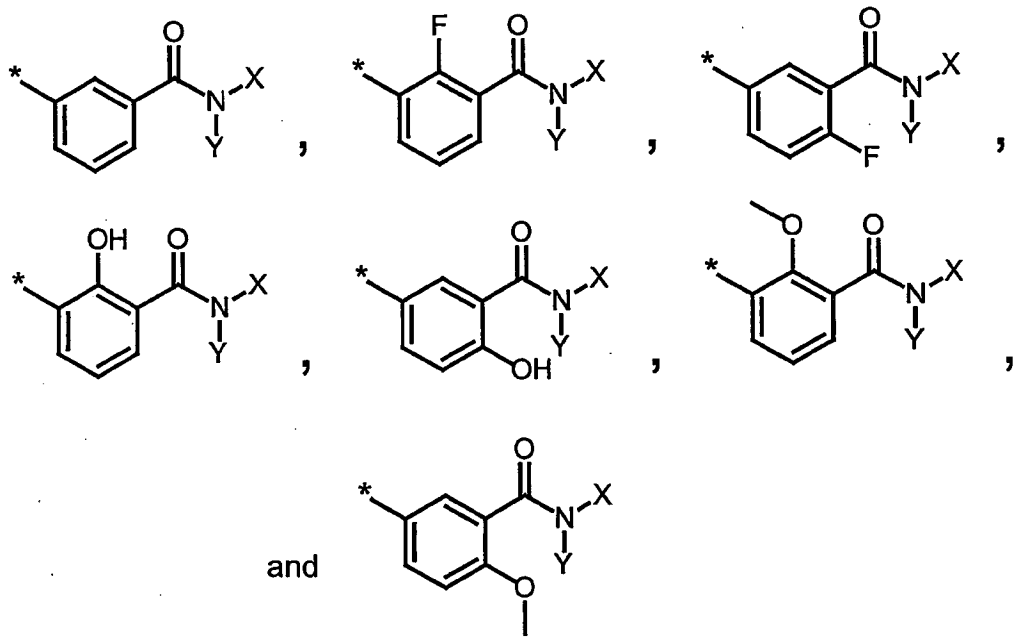


(I')

wherein R^3 to R^5 are defined as described above.

A further alternative embodiment of the present invention relates to a compound of the formula (I), wherein

R^5 denotes a radical of the formula selected from the group consisting of:



and

A further alternative embodiment of the present invention relates to a compound of the formula (I), wherein

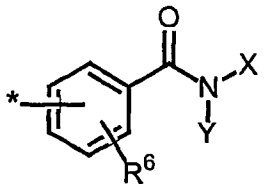
x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote hydrogen, C_{1-4}-alkyl or CF_3 or
R^1 and R^2 together form a C_{1-4}-alkylene bridge;

R^3 and R^4 independently from each other denote C_{1-4}-alkyl;

R^5 denotes a monovalent radical of the formula



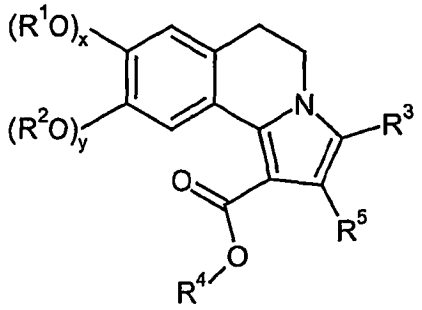
wherein

X and Y independently from each other denote
hydrogen,
C_{1-4}-alkyl optionally substituted with furyl which can be further substituted with 1 to 2 substituents methyl, or
C_{3-8}-cycloalkyl
or

X and Y together with the nitrogen atom to which they are attached, form piperazinyl optionally further substituted (i) with 1 to 2 substituents C_{3-8}-cycloalkyl or (ii) with 1 to 2 substituents C_{1-4}-alkyl optionally further substituted with 1 substituent C_{3-8}-cycloalkyl;

and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

Compounds (I) wherein the radicals $(R^1O)_x$ and $(R^2O)_y$ are attached to the phenyl ring in the following positions, are preferred:



Depending on the substitution pattern, the compounds of the formula (I) according to the invention can exist in stereoisomeric forms which are either like image and mirror image (enantiomers) or are not like image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and to their respective mixtures. The racemic forms, like the diastereomers, can be separated in a known manner into the stereoisomerically uniform components.

Furthermore, certain compounds of the formula (I) can be present in tautomeric forms. This is known to the person skilled in the art, and such compounds are likewise included in the scope of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutically acceptable salts according to the invention are non-toxic salts which in general are accessible by reaction of the compounds (I) with an inorganic or organic base or acid conventionally used for this purpose. Non-limiting examples of pharmaceutically acceptable salts of compounds (I) include the alkali metal salts, e.g. lithium, potassium and sodium salts, the alkaline earth metal salts such as the magnesium and calcium salts, the quaternary ammonium salts such as, for example, the triethyl ammonium salt, acetates, benzene sulphonates, benzoates, dicarbonates, disulphates, ditartrates, borates, bromides, carbonates, chlorides, citrates, dihydrochlorides, fumarates, gluconates, glutamates, hexyl resorcinates, hydrobromides, hydrochlorides, hydroxynaphthoates, iodides, isothionates, lactates, laurates, malates, maleates, mandelates, mesylates, methylbromides,

methylnitrates, methylsulphates, nitrates, oleates, oxalates, palmitates, pantothenates, phosphates, diphosphates, polygalacturonates, salicylates, stearates, sulphates, succinates, tartrates, tosylates, valerates, and other salts used for medicinal purposes.

According to the invention, "hydrates" are forms of the compounds of the formula (I) above which, in the solid or liquid state, form a molecular compound (solvate) by hydration with water. Examples of hydrates are sesquihydrates, monohydrates, dihydrates and trihydrates. Equally suitable are the hydrates of salts of the compounds according to the invention.

In the context of the present invention, the substituents, if not stated otherwise, in general have the following meanings:

Halogen represents fluorine, chlorine, bromine and iodine. Preference is given to chlorine and fluorine.

C_1-C_6-Alkyl per se as well as the prefixes "alkyl" and "alk" in the terms "alkylcarbonyl", "alkoxy", and "alkoxycarbonyl" represents a straight-chain or branched alkyl radical preferrably having from 1 to 6 carbon atoms. Examples which may be mentioned are: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, *n*-octyl and *n*-decyl. The corresponding alkyl groups having fewer carbon atoms, such as, for example, C_1-C_4-alkyl, are derived analogously from this definition.

C_3-C_8-Cycloalkyl represents a mono- or bicyclic alkyl radical having 3 to 8 carbon atoms. Examples which may be mentioned are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. The corresponding cycloalkyl groups having fewer carbon atoms, such as, for example, C_3-C_6-cycloalkyl, are derived analogously from this definition.

Non-limiting examples of C_1-C_6-alkoxycarbonyl radicals include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl and isobutoxycarbonyl. The corresponding alkoxycarbonyl groups having fewer carbon atoms, such as, for example, C_3-C_6-alkoxycarbonyl, are derived analogously from this definition.

C_1-C_6-Alkoxy represents a straight-chain or branched alkoxy radical having 1 to 6 carbon atoms. Examples which may be mentioned are: methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *tert*-butoxy, *n*-pentoxy and *n*-hexoxy. The corresponding alkoxy groups having fewer carbon atoms, such as, for example, C_1-C_4-alkoxy, are derived analogously from this definition.

C_1-C_6-Dialkylamino represents an alkylamino radical having two (independently selected) alkyl substituents, illustratively and preferably representing *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-t-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

C_6-C_{10}-Aryl represents an aromatic radical preferably having 6 to 14, more preferably 6 to 10 carbon atoms. Non-limiting examples of C_6-C_{10}-aryl radicals include phenyl, and naphthyl.

Heteroaryl in the context of the invention represents a preferably 5- to 13-membered heteroaryl or a 5- to 13-membered aromatic heterocycle having from 1, up to 4, heteroatoms from the group consisting of N, O and S, which ring or ring system can be linked via a carbon atom or a nitrogen atom, if such an atom is present. Examples which

may be mentioned are: pyridyl, pyridyl N-oxide, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl or isoxazolyl, indolicenyl, indolyl, benzo[b]thienyl, benzo[b]furyl, benzothiadiazolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl, quinazolinyl. Preferred examples include pyrazolyl, pyrazinyl, pyrrolyl, imidazoyl, triazolyl, indolyl, pyridyl, pyridyl-N-oxide, pyrimidyl, pyridazinyl, furyl, imidazolyl and thienyl.

Heterocycle in the context of the invention represents a preferably 3- to 13-membered saturated or partially unsaturated heterocycle having from 1, up to 4, heteroatoms from the group consisting of N, O and S, which ring or ring system can be linked via a carbon atom or a nitrogen atom, if such an atom is present. Examples which may be mentioned are: tetrahydropyranyl, aziridyl, azepanyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, piperidinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, azepinyl, and 1,4-diazepinyl. Preference is given to azepanyl, piperazinyl, piperidinyl, morpholinyl and pyrrolidinyl.

C_{1-4}-Alkylene or C_{1-4}-alkylene bridge represents a linear or branched, bivalent alkylene radical preferably having 1 to 4 carbon atoms, also known as alkandiyl. Non-limiting examples include methylene, ethylene, propylene, α-methylethylene, ß-methylethylene, α-ethylethylene, ß-ethylethylene, butylene, α-methylpropylene, ß-methylpropylene, and γ-methylpropylene.

C_5-C_{10}-Bridged bicycloalkyl represents a bicyclic alkyl radical having 5 to 10 carbon atoms also containing an alkylene bridge. Non-limiting examples include [2.2.1]bicycloheptane, [2.2.2]bicyclooctanetane, [2.1.1]bicyclohexane, [3.3.1]bicyclononane, and [3.3.2]bicyclodecane.

A ring system represents a mono-, bi- or tricyclic system of fused rings. These rings share two ring members. These ring members are preferably adjacent ([0]-bridge). Non limiting examples include naphthalene, benzo[2,3]dioxolyl, 2,3-dihydrobenzo[1,4]dioxinyl, and indole.

A * symbol next to a bond denotes the point of attachment in the molecule.

The compounds according to the invention exhibit an unforeseeable, useful pharmacological and pharmacokinetic activity spectrum. They are therefore suitable for use as medicaments for the treatment and/or prophylaxis of disorders in humans and animals.

The compounds of this invention may be formulated as a solution of lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or in buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxycellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium acetate.

Alternatively, the compounds of the present invention may be encapsulated, tableted, or incorporated into an emulsion (oil-in-water or water-in-oil) syrup for oral administration. Pharmaceutically acceptable solids or liquid carriers, which are generally known in the pharmaceutical formulary arts, may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch (corn or potato), lactose, calcium sulfate dihydrate, terra alba, croscarmellose sodium,

magnesium stearate or stearic acid, talc, pectin, acacia, agar, gelatin, maltodextrins and microcrystalline cellulose, or colloidal silicon dioxide. Liquid carriers include syrup, peanut oil, olive oil, corn oil, sesame oil, saline, and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 10 mg to about 1 g per dosage unit.

The dosage ranges for administration of the heterocyclics disclosed in this invention are those to produce the desired affect. The dosage will generally vary with age, body weight, extent of the disease, and contraindications, if any. The dosage will also be determined by the existence of any adverse side effects that may accompany the compounds. It is always desirable, whenever possible, to keep adverse side effects to a minimum. One skilled in the art can easily determine the appropriate dosage, scheduling, and method of administration for the exact formulation of the composition being used in order to achieve the desired effective concentration in the individual patient. However, the dosage can vary from between about 1 mg/kg/day to about 500 mg/kg/day, and preferable from between about 1 mg/kg/day to about 50 mg/kg/day.

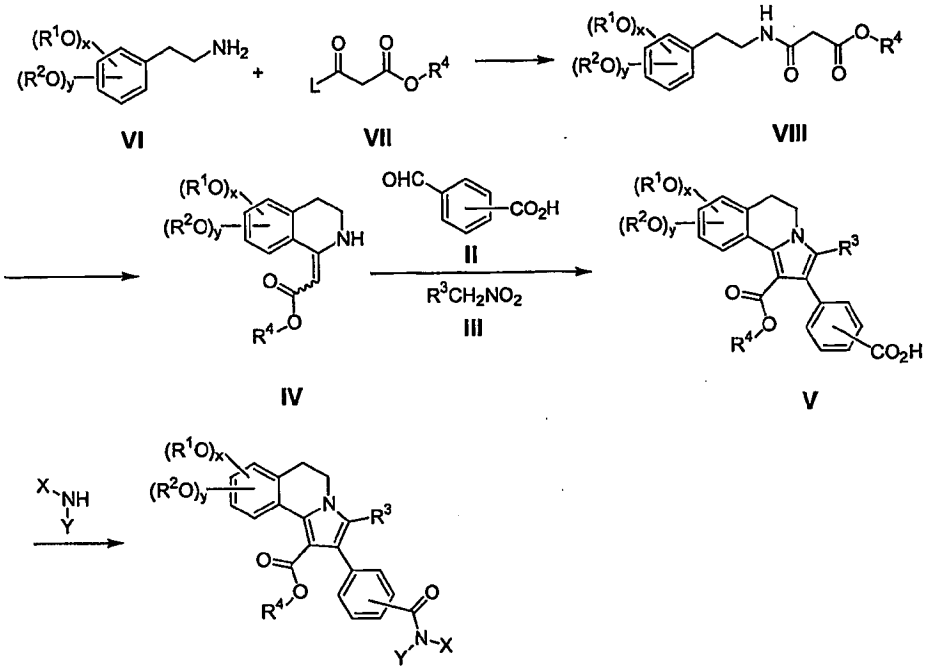
One skilled in the art will recognize that modifications may be made in the present invention without deviating from the spirit or scope of the invention. The invention is illustrated further by the following experimental information and examples, which are not to be construed as limiting the invention in spirit or scope to the specific procedures or compositions described in them.

The present invention also relates to a process for making the compounds. The compounds of the invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented for synthesis of the 2-substituted pyrrolo[2.1-a]isoquinoline compounds of the present invention, with more detailed particular examples being presented below in the experimental section describing the working examples. Variables are defined above in the general description.

The processes can be illustrated by the following scheme 1:

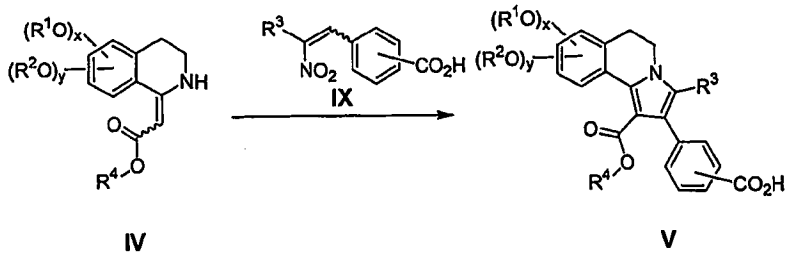
General Method A:

General Method A1



The compounds (I) can be synthesized according to the reaction sequence shown in Method A1 above. Thus, the compounds (VIII) can be synthesized by reacting amino compounds (VI) with compounds (VII), wherein L is a leaving group, for example a halogen radical such as Cl, or a radical of the formula $-OC(O)R^5$, wherein R^5 is defined as optionally substituted C_{1-4}-alkyl or $-CH_2C(O)OR^4$. Compounds (IV) are obtained by reacting compounds (VIII) with a dehydrating agent such as, e.g., phosphorous pentoxide. Reacting compounds (IV) with carboxybenzaldehydes (II) and R^3-CH_2-NO_2 (III) provides compounds (V). Reacting the carboxy compounds (V) with the amine HNXY furnishes the amides (I).

General Method A2

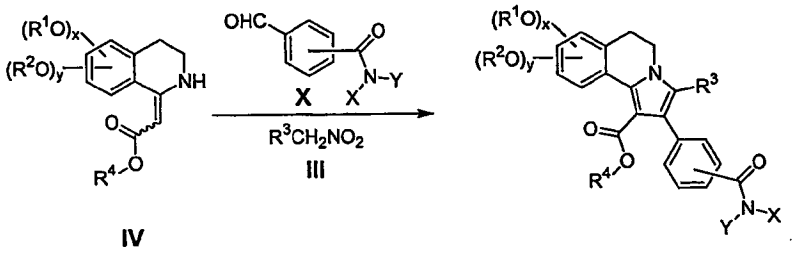


IV V

Alternatively, the transformation of compounds (IV) into compounds (V) in Method A1 can be accomplished with the conditions shown in General Method A2. Thus, treatment of compounds (IV) with compounds (IX) provides compounds (V).

General Method B:

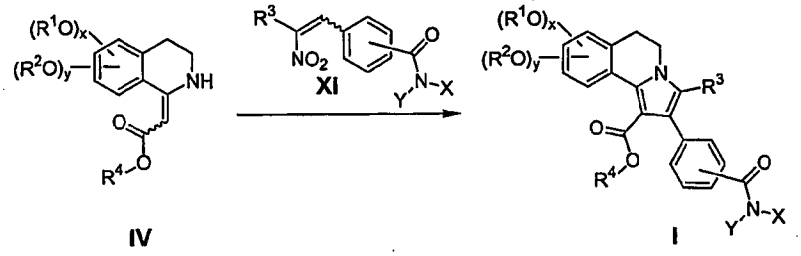
General Method B1



IV I

The compounds (IV) can also be directly converted to the compounds (I) according to the General Method B1. Thus, treatment of compounds (IV) with compounds (X) and (III) gives compounds (I).

General Method B2



IV I

Alternatively, the transformation of compounds (IV) into compounds (I) can be accomplished with the conditions shown in General Method B2. Thus, treatment of compounds (IV) with compounds (XI) furnishes compounds (I).

The compounds (VI) are commercially available or can be synthesized according to methods commonly known to those skilled in the art (H. Mayer et al., Heterocycles 31, 1035 (1990); E. Müller (ed.), "Methoden der Organischen Chemie" (Houben-Weyl), 4th ed., Vol. 11/1 Stickstoff-Verbindungen II, Georg Thieme Verlag, Stuttgart 1957; Shepard et al. in J. Org. Chem. 17, 568 (1952) and in J. Am. Chem. Soc. 72, 4364 (1950)).

The compounds (VII) are commercially available or can be synthesized according to methods commonly known those skilled in the art [e.g. via acylation of acetic acid with an alkyl chloroformate or dialkyl carbonate (March, Advanced Organic Chemistry, 3rd ed., p. 440-441, Wiley 1985) and converting the resulting monoester of malonic acid into e.g. the corresponding acid chloride or anhydride by methods commonly known to those skilled in the art (see e.g. March, Advanced Organic Chemistry, 3rd ed., p. 355, 388, Wiley 1985)].

The reaction between the compounds (VI) and (VII) is preferably carried out in a solvent. Suitable solvents comprise the customary organic solvents which are inert under the reaction conditions. Non-limiting examples include ethers such as diethyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxy ethane; hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane, mineral oil fractions; halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene; ketones such as acetone; esters such as ethyl acetate; nitriles such as acetonitrile; heteroaromatics such as pyridine; polar solvents such as dimethyl formamide and hexamethyl phosphoric acid tris-amide; and mixtures of the above-mentioned solvents. Dichloromethane is frequently used.

The compounds (VII) are generally employed in an amount of from 1 to 4 mol per mol of compounds (VI); an equimolar amount or slight excess of compounds (VII) is preferred.

The reaction between the compounds (VI) and (VII) is preferably carried out in the presence of a base. Non-limiting examples include alkali metal hydrides and alkali metal alkoxides such as, for example, sodium hydride and potassium tert-butoxide; C_1-C_4-alkyl amines such as, for example, triethyl amine; cyclic amines such as, for example, piperidine, pyridine, dimethylamino pyridine and -preferably - 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU). The base is generally employed in an amount of from 1 to 4 mol per mol of compounds (VI); an equimolar amount or slight excess of the base is preferred.

The reaction of the compounds (VI) and (VII) can generally be carried out within a relatively wide temperature range. In general, the reaction is carried out within a range of from -20 to 200°C, preferably from 0 to 70°C, and more preferably at room temperature.

For the cyclization of the compounds (VIII) to yield compounds (IV), dehydrating agents such as, for example, P_2O_5 or $POCl_3$ are generally employed in an amount of from 1 to 10 mol, preferably from 3 to 8 mol, per mol of compounds (VIII).

The cyclization reaction of the compounds (VIII) to yield the compounds (IV) is also preferably carried out in a solvent. Non-limiting examples comprise the customary organic solvents which are inert under the reaction conditions. They preferably include ethers such as diethyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxy ethane; hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane, mineral oil fractions; halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene; esters such as ethyl acetate; ketones such as acetone; nitriles such as acetonitrile; heteroaromatics such as pyridine; polar solvents such as dimethyl formamide and hexamethyl phosphoric acid tris-amide; and mixtures thereof. Toluene is preferred, if the reaction is carried out with P_2O_5, and acetonitrile is preferred, if the reaction is carried out with $POCl_3$ (Benovsky, Stille, Tetrahedron Lett. 38, 8475-8478 (1997)).

The temperature for the cyclization reaction of compounds (VIII) is preferably within a range of from 60 to 200°C and more preferably within a range of from 80 to 120°C.

The above process steps are generally carried out under atmospheric pressure. However, it is also possible to carry them out under superatmospheric pressure or under reduced pressure (for example, in a range of from 0.5 to 5 bar). The reaction time can generally be varied within a relatively wide range. In general, the reaction is finished after a period of from 2 to 24 hours, preferably from 6 to 12 hours.

The compounds (II) are commercially available or can be synthesized according to methods commonly known to those skilled in the art (I.T. Harrison and S. Harrison, Compendium of Organic Synthetic Methods, pp. 132-176, Wiley-Interscience; E. Müller (ed.), " Methoden der Organischen Chemie" (Houben-Weyl), Vol. VII/1 Sauerstoff-Verbindungen II, Georg Thieme Verlag, Stuttgart 1954).

The compounds (III) are commercially available.

The reaction of the compounds (IV) with compounds (II) and (III), or with compounds (X) and (III), or with compounds (IX), or with compounds (XI), can be carried out as a one-pot synthesis, preferably in a solvent. Suitable solvents comprise the customary organic solvents which are inert under the reaction conditions. Non-limiting examples include ethers such as diethyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxy ethane; hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane, mineral oil fractions; halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene; alcohols such as methanol, ethanol, n-propanol, isopropanol; esters such as ethyl acetate; ketones such as acetone; nitriles such as acetonitrile; heteroaromatics such as pyridine; polar solvents such as dimethyl formamide and hexamethyl phosphoric acid tris-amide; and mixtures of the above-mentioned solvents. Ethanol/isopropanol (preferably in an approximate vol/vol-ratio of 1:1) mixtures are preferred.

The compounds (III) are generally employed in an amount of from 1 to 3 mol per mol of compounds (II); an equimolar amount or slight excess of compounds (III) is preferred. The

compounds (IV) are generally employed in an amount of from 0.1 to 1 mol, preferably from 0.3 to 1 mol, per mol of compounds (II). The compounds (IX) or (XI) are generally employed in an amount from 1 to 3 mol per mol of compounds (IV); an equimolar amount or slight excess of compounds (III) is preferred.

The reactions of the compounds (IV) with compounds (II) and (III), or with compounds (X) and (III), or with compounds (IX), or with compounds (XI), are preferably carried out in the presence of a base. Non-limiting examples include alkali metal hydrides and alkali metal alkoxides such as, for example, sodium hydride and potassium tert-butoxide; C_{1-4}-alkyl amines such as, for example, triethyl amine; cyclic amines such as, for example, pyridine, dimethylamino pyridine, 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU) and - preferably - piperidine. The base is generally employed in an amount of from 0,1 to 1 mol, preferably from 0,3 to 1 mol, per mol of compounds (II) or compounds (V), respectively.

The reactions of the compounds (IV) with compounds (II) and (III), or with compounds (X) and (III), or with compounds (IX), or with compounds (XI), are generally carried out within a relatively wide temperature range. In general, they are carried out in a range of from -20 to 200°C, preferably from 0 to 100°C, and more preferably from 50 to 90°C. The steps of this reaction are generally carried out under atmospheric pressure. However, it is also possible to carry them out under superatmospheric pressure or under reduced pressure (for example, in a range of from 0.5 to 5 bar). The reaction time can generally be varied within a relatively wide range. In general, the reaction is finished after a period of from 2 to 24 hours, preferably from 6 to 12 hours.

The compounds HNXY are commercially available or can be synthesized according to methods commonly known those skilled in the E. Müller (Ed.), "Methoden der Organischen Chemie" [Methods of Organic Chemistry] (Houben-Weyl), Vol. 11/1 Stickstoff-Verbindungen, Georg Thieme Verlag, Stuttgart 1957).

The reaction between the compounds (V) and HNXY is preferably carried out in a solvent. Suitable solvents comprise the customary organic solvents which are inert under the reaction

conditions. Non-limiting examples include ethers such as diethyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxy ethane; hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane, mineral oil fractions; halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene; ketones such as acetone; esters such as ethyl acetate; nitriles such as acetonitrile; heteroaromatics such as pyridine; polar solvents such as dimethyl formamide and hexamethyl phosphoric acid tris-amide; and mixtures of the above-mentioned solvents. Dichloromethane and tetrahydrofuran are preferred.

The compounds HNXY are generally employed in an amount of from 1 to 4 mol per mol of compounds (V); an equimolar amount or slight excess of compounds HNXY is preferred.

The reaction between the compounds (V) and HNXY is preferably carried out in the presence of a coupling reagent by methods commonly known to those skilled in the art (see e.g. March, Advanced Organic Chemistry, 4th ed., pp. 419-421 Wiley 1992). Non-limiting examples include dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, N,N'-carbonyldiimidazole, pivaloyl chloride, bis(2-oxo-3-oxazolidinyl)phosphinic chloride and benzotriazol-1-yloxytris(pyrrolidino)- phosphonium hexafluorophosphate. The coupling reagents may optionally be bound to a polymeric resin. The coupling reagent is generally employed in an amount of from 1 to 4 mol per mol of compounds (V); an equimolar amount or slight excess of the reagent is preferred.

Additionally, a promoter may be added to the coupling reaction. Non-limiting examples include 1-hydroxybenzotriazole, N,N'-dimethylaminopyridine, and 3-hydroxy-3H-1,2,3-triazolo[4,5-b]-pyridine. The promoter is generally employed in an amount from 0.1 to 1 mol per mol of compounds (V), preferably from 0.3 to 1 mol, per mol of compounds (V).

The reaction of the compounds (V) and HNXY can generally be carried out within a relatively wide temperature range. In general, the reaction is carried out within a range of from -20 to 200°C, preferably from 0 to 70°C, and generally at room temperature.

Compounds (IX) and (XI) are commercially available or can be synthesized according to methods commonly known to those skilled in the art (H. Feuer (ed.) "The Chemistry of the Nitro and Nitroso Groups" Interscience Publishers, New York, 1969, pp. 76-117).

Compounds (X) are commercially available or can be synthesized by coupling compounds HNXY with compounds (II) in the same manner as described above for the coupling of compounds (V) with compounds HNXY.

Compounds (I) wherein R^3 is hydrogen can be synthesized by General Method A or B using compounds (III) or (V) respectively wherein R^3 is hydrogen.

Optionally, the compounds obtained through General Method A or B can be converted into an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof

The compounds of the present invention are inhibitors of phosphodiesterase 10a (PDE 10a). As outlined above, the inhibition of PDE 10a is a promising approach for the treatment of cancer. The biological tests described below show that the compounds (I) exhibit a pronounced anti-proliferation activity against tumor cells; they are therefore useful for the treatment of cancer. Furthermore, our investigations showed that they are also useful for treatment of conditions of pain and/or for the lowering of the temperature of the body in fever conditions.

The compounds according to the invention can be used as active ingredients for the production of medicaments against carcinomatous disorders. For this, they can be converted into the customary formulations such as tablets, coated tablets, aerosols, pills, granules, syrups, emulsions, suspensions and solutions using inert, non-toxic, pharmaceutically suitable excipients or solvents. Preferably, the compounds according to the invention are used in an amount such that their concentration is approximately 0.5 to approximately 90% by weight, based on the ready-to-use formulations, the concentration being dependent, inter alia, on the indication of the medicament.

The formulations can be produced, for example, by extending the active compounds with solvents and/or excipients having the above properties, where, if appropriate, additionally emulsifiers or dispersants and, in the case of water as the solvent, an organic solvent can additionally be added.

Administration can be carried out in a customary manner, preferably orally, transdermally or parenterally, for example perlingually, buccally, interperitoneally, intravenously, nasally, rectally or inhalationally.

For human use, in the case of oral administration, it is recommended to administer doses of from 0.001 to 50 mg/kg, preferably from 0.01 to 20 mg/kg. In the case of parenteral administration such as, for example, intravenously or via mucous membranes nasally, buccally or inhalationally, it is recommended to use doses of from 0.001 to 0.5 mg/kg.

If appropriate, it may be necessary to depart from the amounts mentioned above, namely depending on the body weight or the type of administration route, on the individual response towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the above mentioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be recommended to divide these into several individual doses over the course of the day.

The compounds according to the invention are also suitable for use in veterinary medicine. For use in veterinary medicine, the compounds or their non-toxic salts can be administered in a suitable formulation in accordance with general veterinary practice. Depending on the kind of animal to be treated, the veterinary surgeon can determine the nature of use and the dosage.

The present invention provides compounds for the use in a medical application, in particular for combating cancer.

The invention further provides a method of manufacturing a pharmaceutical composition by combining at least one of the compounds of the invention with at least one pharmacologically acceptable formulating agent.

The invention further provides a pharmaceutical composition comprising as an active ingredient an effective amount of at least one of the compounds of the invention and at least one pharmacologically acceptable formulating agent.

The invention further provides a pharmaceutical composition comprising as an active ingredient an effective amount of at least one of the compounds of the invention and at least one pharmaceutical active ingredient which is different from the compounds of the invention.

The invention further provides a medicament in dosage unit form comprising an effective amount of a compound according to the invention together with an inert pharmaceutical carrier.

The invention further provides a method of combating cancer in mammals comprising administering to a mammal in need thereof an antiproliferative effective amount of at least one compound according to the invention either alone or in admixture with a diluent or in the form of a medicament.

The percentages in the description above, in the following tests and in the Examples are - if not stated otherwise - percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentrations in solutions of liquids in liquids are ratios by volume.

A. Examples

Abbreviations used in this specification

BSA	bovine serum albumin
™Cremophor®	non-ionic emulsifier from BASF, Germany
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMEM	Dulbecco's Modified Eagle Medium, Life Technologies, Gaithersburg, MD, U.S.A.
DMF	N,N-dimethyl formamide
DMSO	dimethyl sulphoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA	ethylene diamine tetraacetate
FBS	fetal bovine serum
HEPES	N-(2-hydroxyethyl)-piperazine-N'-(2-ethane sulphonic acid)
HPLC	high pressure liquid chromatography
LC-MS	liquid chromatography – coupled mass spectroscopy
LC RT	liquid chromatography retention time
LDH	lactate dehydrogenase
MP	melting point
NMR	nuclear resonance spectroscopy
PBS	phosphate-buffered saline
PyBOP	Bromotripyrrolidinophosphonium hexafluorophosphate
TLC	thin layer chromatography
Tris/hydrochloric acid	tris(hydroxymethyl)-aminomethane hydrochloride
™Triton X-100®	tert.-octyl-phenoxypolyethoxyethanol, Rohm& Haas, USA

The yield percentages of the following examples refer to the starting component which was used in the lowest molar amount.

LC-MS / HPLC methods:

Method A:

MS equipment:	Finnigan LCQ Ion Trap Mass Spectrometer			
	ionisation mode:	ESI		
HPLC equipment:	HP 1100			
	UV detection:	254 nm		
Column:	YMC pro C-18			
	23 mm x 2 mm	120 Å		
Supplier:	YMC			
Gradient:	Time [min.]	A: %	B: %	Flow [mL/min.]
	0.50	90.0	10.0	1.0
	3.50	5.0	95.0	1.0
	4.00	5.0	95.0	1.0
	4.01	90.0	10.0	1.0
	6.50	90.0	10.0	1.0

A: 0.02 % strength solution of trifluoroacetic acid in 2 % acetonitrile / 98 % water

B: 0.018 % strength solution of trifluoroacetic acid in 98 % acetonitrile / 2 % water

Method B:

MS equipment:	Micromass LCZ			
	ionisation mode:	ESI		
HPLC equipment:	Gilson 215			
	UV detection:	254 nm		
Column:	YMC pro C-18			
	23 mm x 2 mm	120 Å		
Supplier:	YMC			
Gradient:	Time [min.]	A: %	B: %	Flow [mL/min.]
	0.50	90.0	10.0	1.0
	3.50	5.0	95.0	1.0
	4.00	5.0	95.0	1.0
	4.01	90.0	10.0	1.0
	4.80	90.0	10.0	1.0

A: 0.02 % strength solution of trifluoroacetic acid in 2 % acetonitrile / 98 % water

B: 0.02 % strength solution of trifluoroacetic acid in 98 % acetonitrile / 2 % water

Method C:

Column: Kromasil RP-18

60 mm x 2.0 mm 3.5 µm

Gradient:

Time [min.]	A: %	B: %	Flow [mL/min.]
0.00	98.0	2.0	0.75
4.50	10.0	90.0	0.75
6.50	10.0	90.0	0.75

A: 0.5% strength aqueous $HClO_4$

B: acetonitrile

Method D:

MS equipment: Micromass Platform LCZ

ionisation mode: ESI positive / negative

HPLC equipment: HP 1100

UV detection: 208-400 nm

temperature: 40 °C

Column: Symmetry C 18

50 mm x 2.1 mm 3.5 µm

Supplier: Waters

Gradient:

Time [min.]	A: %	B: %	Flow [mL/min.]
0.00	90.0	10.0	0.50
4.00	10.0	90.0	0.50
6.00	10.0	90.0	0.50

A: 0.05% strength solution of formic acid in water

B: 0.05% strength formic acid in acetonitrile

Method E:

MS equipment: Finnigan MAT 900S

ionization mode: ESI - positive

HPLC equipment: Thermo Separation Products

P4000, AS3000, UV3000HR

UV detection: 210 nm

temperature: 70 °C

Column: ™Symmetry C 18

50 mm x 2.1 mm 3.5 µm

Supplier: Waters

Gradient:

Time [min.]	A: %	B: %	C: %	Flow [mL/min.]
0.00	2.0	49.0	49.0	0.9
2.50	95.0	2.5	2.5	1.2
5.00	95.0	2.5	2.5	1.2
5.50	2.0	49.0	49.0	1.2
6.50	2.0	49.0	49.0	1.2
7.00	2.0	49.0	49.0	0.9

A: acetonitrile

B: 0.01% HCl in water

C: water

Method F:

MS equipment: Micromass Quattro LCZ

ionisation mode: ESI positive / negative

HPLC equipment: HP 1100

UV detection: 208-400 nm

temperature: 40 °C

Column: ™Symmetry C 18

50 mm x 2.1 mm 3.5 µm

Supplier: Waters

Gradient:

Time [min.]	A: %	B: %	Flow [mL/min.]
0.00	90.0	10.0	0.50
4.00	10.0	90.0	0.50
6.00	10.0	90.0	0.50

A: 0.05% strength solution of formic acid in water

B: 0.05% strength formic acid in acetonitrile

Method G:

HPLC Equipment: Gilson 215

UV Detection: 220 and 254 nM

Temperature: 25 °C

Column: ™YMC-Pack Pro C18

50 mm x 4.6 mm 5µM

Supplier: Waters

Gradient:	Time [min.]	A: %	B: %	Flow [mL/min]
	0.00	10.0	90.0	4.00
	3.50	90.0	10.0	4.00
	4.50	90.0	10.0	4.00
	4.60	10.0	90.0	4.00
	5.00	10.0	90.0	4.00

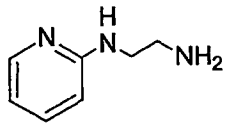
A: 0.1% strength solution of TFA in acetonitrile

B: 0.1% strength aqueous TFA

Starting Materials

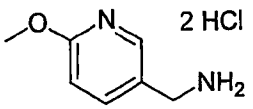
For amines not commercially available the specific preparations are exemplified below:

***N*-(2-Aminoethyl)-*N*-(2-pyridinyl)amine**



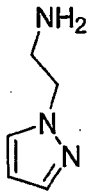
A solution of 2-bromopyridine (1.0 g, 6.3 mmol) and ethylenediamine (2.0 mL, 29.8 mmol) was heated to 120 °C for 18 h. The reaction mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give an oil (775 mg, 90%): **MS** (HPLC/ES): m/z = 138.1 (M + 1); **LCMS RT** (method A): 0.75 min.

(6-Methoxy-3-pyridinyl)methanamine dihydrochloride



2-Methyoxypyridine-5-carbonitrile (2.0 g, 14.9 mmol) was added to 10% Pd/C (200 mg, 10% w/w), ethanol (100mL) and conc. hydrochloric acid (3 mL) in a 500 ml bottle under argon and subjected to 58 psi on a Parr Shaker for 40 h. The reaction mixture was filtered through a pad of Celite® and washed with ethanol. The solution was concentrated *in vacuo* to give a solid: **MS** (HPLC/ES): m/z = 138.9 (M + 1); **LCMS RT** (method A): 0.72 min. The amine was carried on to amide coupling conditions without further purification.

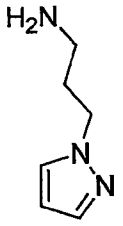
2-(1H-Pyrazol-1-yl)ethylamine



To a solution of 1.50 g (22.0 mmol) 1*H*-pyrazole in 50 mL of acetonitrile was added 3.35 g (83.7 mmol) of powdered sodium hydroxide and 299 mg (0.88 mmol) of tetrabutylammoniumsulfate. The reaction was stirred for 30 min and 3.07 g (26.4 mmol) of 2-chloroethylamine hydrochloride was added. This was stirred at room temperature for 3 d, at which time TLC analysis (silica gel 60, 90:10 dichloromethane/methanol, iodine staining) suggested complete reaction. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was cooled to 0 °C and 15 mL of 40 % strength hydrobromic acid was added slowly. An equal portion of ethanol was then added and the

biphasic solution was heated to form only one phase. The resulting solution was cooled to 0 °C and slowly triturated with ether to form 4.21 g (21.9 mmol, 99 %) of 2-(1H-pyrazol-1-yl)ethylamine as a white solid: **^{1}H-NMR** (DMSO-d_6) δ 3.24 (sextet, J = 6.0, 2H), 4.40 (t, J = 5.9, 2H), 6.00 (br s, 3H), 6.28 (t, J = 2.1, 1H), 7.50 (d, J = 1.7, 1H), 7.77 (d, J = 2.3, 1H), 7.92 (br s, 2H); **MS** (HPLC/ES) m/z = 112.1 (M + 1); **LCMS RT**(method B): 0.79 min.

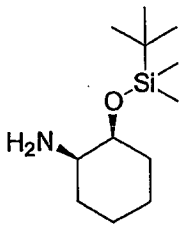
3-(1H-Pyrazol-1-yl)-propylamine



This compound was prepared in the manner shown for 2-(1H-pyrazol-1-yl)ethylamine above.

1.50 g (7.28 mmol, 99 %) of 2-(1H-pyrazol-1-yl)propylamine as a white solid: **^{1}H-NMR** (DMSO-d_6) δ 2.02 (m, 2H), 2.73 (m, 2H), 4.19 (t, J = 6.4, 2H), 6.23 (t, J = 2.2, 1H), 7.44 (dd, J = 0.7, 1.9, 1H), 7.72 (m, 4H); **MS** (HPLC/ES) m/z = 126.1 (M + 1); **LCMS RT** (method B): 0.80 min.

cis-2-{[tert-Butyl-(dimethyl)-silyl]-oxy}cyclohexylamine

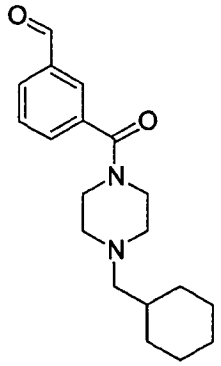


To a suspension of cis-2-aminocyclohexanol (1.00 g, 8.68 mmol) in dichloromethane (6 mL) at 0 °C was added 2,6-lutidine (1.86 g, 17.36 mmol) and t-butyldimethylsilyltriflate (3.44 g, 13.0 mmol) dropwise. The mixture was stirred overnight and concentrated *in vacuo*. The residue was diluted with ether, washed with water, and dried over magnesium sulfate. The solvent was removed *in vacuo* to give 2.0 g (100%) of a white solid.

Resolution of 1-(4-fluorophenyl)ethylamine. (1R)-1-(4-fluorophenyl)-ethylamine and (1S)-1-(4-fluorophenyl)-ethylamine

Racemic 1-(4-fluorophenyl)-ethylamine (commercially available) was resolved by (+)-tartaric acid following the procedures of A. Ault (*Org. Synth.*, 1973, Coll. Vol. 5, 932) and S. Takenaka et al. (*J.C.S. Perkin II*, 1978, 95).

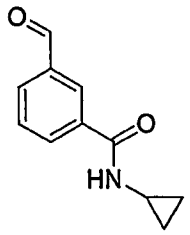
3-[4-(Cyclohexylmethyl)-piperazine-1-carbonyl]-benzaldehyde



To a solution of 3-carboxybenzaldehyde (500 mg, 3.33 mmol) in tetrahydrofuran (10 mL) was added PyBOP(2.25 g, 4.33 mmol) and N,N-diisopropylethylamine (750 μL, 4.33 mmol). The reaction mixture was stirred for 20 min, after which 1-cyclohexylmethylpiperizine (789 mg, 4.33 mmol) was added. The reaction mixture was

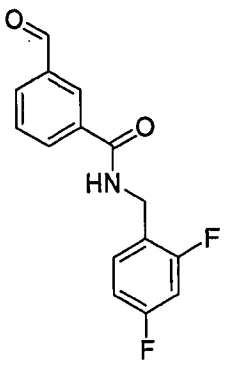
stirred for 18h, at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested almost complete conversion to the amide. The reaction was concentrated *in vacuo*, and the resulting crude product was purified by using the Biotage Quad4 (25 M column) eluting with 35:65 ethyl acetate/hexanes. The desired fractions were collected and concentrated *in vacuo* to afford the title compound as a yellow oil which turned pink upon standing (563 mg, 1.79 mmol, 54%): **^{1}H-NMR** ($CDCl_3$) δ 10.02 (s, 1H), 7.91 (m, 2H), 7.66 (m, 1H), 7.26 (m, 1H), 3.81 (br. s., 2H), 3.42 (br. s., 2H), 2.50 (br. s., 2H), 2.36 (br. s., 2H), 2.17 (d, J = 6.8 Hz, 2H), 1.73 (m, 6H), 1.51 (m, 1H), 1.21 (m, 2H), 0.86 m, 2H).

3-Formyl-N-cyclopropyl-benzamide



To a solution of 3-carboxybenzaldehyde (500 mg, 3.33 mmol) in tetrahydrofuran (5 mL) was added PyBOP (2.25 g, 4.33 mmol) and N,N-diisopropylethylamine (750 µL, 4.33 mmol). The reaction mixture was stirred for 20 min, after which cyclopropylamine (300 µL, 4.33 mmol) was added. The reaction mixture was stirred for 18h, at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* and purified *via* column chromatography eluting with 2:1 – 3:1 ethyl acetate/hexanes, which afforded the title compound as a white solid (534 mg, 2.82 mmol, 85%): **^{1}H-NMR** (DMSO, d^6) δ 10.03 (s, 1H), 8.65 (m, 1H),8.31 (m, 1H), 8.10 (m, 1H), 8.02 (m, 1H), 7.66 (t, J = 7.6 Hz, 1H), 2.87 (m, 1H), 0.71 (m, 2H), 0.59 (m, 2H); **HPLC RT** (Method G): 1.20 min.

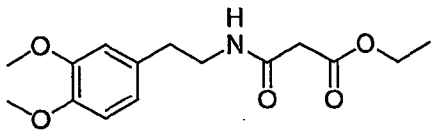
3-formyl-N-(2,4-difluorobenzyl)-benzamide



To a solution of 3-carboxybenzaldehyde (500 mg, 3.33 mmol) in tetrahydrofuran (10 mL) was added PyBOP (2.25 g, 4.33 mmol) and N,N-diisopropylethylamine (750 μL, 4.33 mmol). The reaction mixture was stirred for 20 min, after which 2,4-difluorobenzylamine (510 μL, 4.33 mmol) was added. The reactoin mixture was stirred for 18h, at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* and purified *via* prep HPLC eluting with 40-90% acetonitrile/water over 3.5 minutes to afford 733 mg (2.66 mmol, 80%) of RDB 121-1 as a white solid: **^{1}H-NMR** (DMSO, d^6) δ 10.05 (s, 1H), 9.25 (t, J = 5.7 Hz, 1H), 8.39 (m, 1H), 8.17 (m, 1H), 8.06 (dt, J = 7.6, 1.3 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.43 (m, 1H), 7.23 (m, 1H), 7.05 (m, 1H), 4.49 (d, J = 5.5 Hz, 2H).

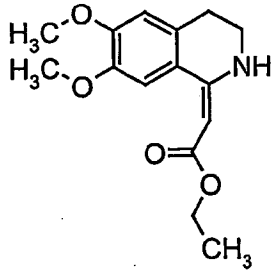
Intermediates

1.1. Ethyl 2-{N-[2-(3,4-dimethoxyphenyl)-ethyl]-carbamoyl} acetate



A solution of 50.0 g (275.9 mmol) of 3,4-dimethoxyphenethylamine in 500 mL of dichloromethane was treated with 42.0 g (275.9 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene, followed by dropwise addition of 35.0 mL (41.6 g, 276.4 mmol) of ethyl malonyl chloride at a rate that kept the internal temperature below 30 °C. The resultant clear yellow solution was stirred at room temperature under an argon atmosphere for 16 h, at which time TLC analysis (silica gel 60, 5:95 methanol/dichloromethane, UV detection) suggested complete reaction. The organics were washed with brine (3 X 1000 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was dried under high vacuum at 30 °C for 24 h to provide 80.6 g (272.8 mmol, 99%) of a yellow oil: **^{1}H-NMR** (DMSO-d_6): δ = 1.16, 1.18 (t, mixture of rotamers; J = 7.0, 3H), 2.63 (t, J = 7.7, 2H), 3.18 (s, 2H,), 3.25 (m, 2H), 3.70 (s, 3H), 3.73 (s, 3H), 4.05 (q, J = 7.0, 2H), 6.69 (dd, J = 2.2, 8.4, 1H), 6.79 (d, J = 2.2, 1H), 6.83 (d, J = 8.4, 1H), 8.1 (br t, 1H, J = 5.4); **MS** (HPLC/ES): m/z = 296 (M + 1); **TLC** (10:90 methanol/dichloromethane, UV detection): R_f = 0.70.

1.2. Ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate

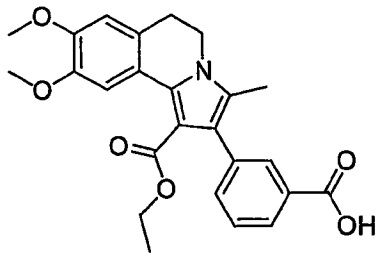


To a refluxing solution of methanesulfonic anhydride (648.83 g, 3.72 mol) in toluene (4 L) was added Intermediate 1.1, ethyl 2-{N-[2-(3,4-dimethoxyphenyl)ethyl]-carbamoyl}-acetate, (1000 g, 3.39 mol) portionwise over 20 minutes. The reaction was stirred at reflux for 30 minutes at which point the heat was removed and the toluene was decanted. The resulting dark oil was then dissolved in water (3000 mL) and treated portionwise with solid potassium carbonate until a pH of about 8 was achieved. The organic material was extracted from the dark biphasic mixture using ethyl acetate (3000 mL). The combined organic extracts were washed with brine (3 x 2000 mL) and concentrated to 1/3 volume.

The resultant dark oil was placed on a pad of silica gel 60 (400 cc) and eluted using ethyl acetate/hexane (1:1). The desired fractions were concentrated to a yellow oil which was seeded with a small amount of crystals of the title compound and placed in a refrigerator overnight. The yellow crystalline solid which formed was filtered, washed with ethyl acetate/ hexane (1:1) (2 x 50 ml), and vacuum dried for 12 hours to give 533.26 g of the desired product . The filtrate was concentrated to a dark oil and seeded a second time. After 1 hour, the newly formed yellow solid was filtered, washed with ethyl acetate/ hexane (1:1) (2 x 50 ml), and vacuum dried for 12 hours to provide 106.23 g of a second crop . The two batches of crystals were combined to provide the title compound (639.49 g, 68 %). **^{1}H-NMR** (DMSO-d_6): δ 1.18 (t, J = 7.0 Hz, 3H); 2.76 (t, J = 6.5 Hz, 2); 3.36 (m, 2H); 3.78 (s, 6H); 4.02 (q, J = 7.0 Hz, 2H); 5.05 (s, 1H); 6.87 (s, 1H); 7.15 (s, 1H); 8.95 (bs, 1H). **MS** (HPLC/ES; method A): m/z = 278 (M + 1). **TLC** [ethyl acetate/hexane (1:1)]: R_f = 0.63

Instead of methanesulfonic anhydride also phosphorous pentoxide can be used according to this method.

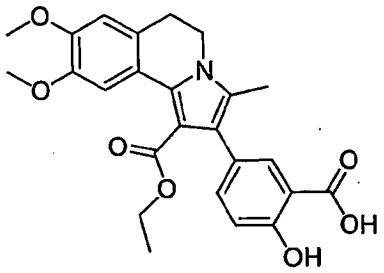
1.3. Ethyl 2-(3-carboxyphenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



5.18 mL (72.1 mmol) of nitroethane, 8.56 mL (86.5 mmol) of piperidine, and 10.8 g (72.1 mmol) of 3-carboxy-benzaldehyde were added to a solution of 10 g (36.06 mmol) of ethyl 2-(6,7-dimethoxy-2,3,4-trihydro-isoquinolylidene)-acetate (Intermediate 1.2.) in 300 mL of isopropanol/ ethanol (1:1 v/v). The solution was heated at reflux for 16 h. Subsequently, the mixture was cooled to room temperature, and the volatiles were removed *in vacuo*.

The resultant solid was suspended in 150 mL of 1 N hydrochloric acid, and the aqueous mixture was extracted with trichloromethane (3 X 75 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the crude product as an orange solid, which was purified by trituration with ether (14 g, 89 %): **^{1}H-NMR** (DMSO-d_6): $\delta = 0.81$ (t, $J = 6.9$, 3H), 2.13 (s, 3H), 2.95 (t, $J = 6.5$, 2H), 3.72 (s, 3H) 3.78 (s, 3H), 3.90-3.96 (m, 4H), 6.93 (s, 1H), 7.40-7.49 (m, 2H), 7.72 (d, $J = 1.3$, 2H), 7.81 (m, 1H); **MS** (HPLC/ES): m/z = 436 (M + 1).

2.1. 5-[1-(ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-hydroxybenzoic acid

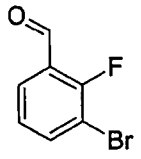


A suspension of ethyl 2-(6,7-dimethoxy-2,3,4-trihydro-isoquinolylidene)-acetate (11.67 g, 42.08 mmol, Intermediate 1.2.) and 5-formylsalicylic acid (14.0 g, 84.27 mmol) in dry ethanol (175 mL) and 2-propanol (175 mL) was treated with nitroethane (6.37 g, 84.85 mmol) and piperidine (8.62 g, 101.23 mmol). The contents were heated at reflux under argon for 12 h, at which time TLC analysis (silica gel 60, 10% methanol/dichloromethane, UV detection) suggested complete reaction. The contents were concentrated *in vacuo* and the dark residue was dissolved in dichloromethane (500 mL). The organics were washed with 1.0 N aqueous hydrochloric acid (150 mL) in brine (200 mL) and the layers were separated. Concentration of the organic phase to ~150 mL effected precipitation of a yellow solid. The crude material was filtered, dissolved in hot 10% methanol/ethyl acetate (300 mL), and allowed to cool to room temperature. The contents were further cooled to 3 °C for 2 h, and the resultant precipitate was filtered and dried under high vacuum at 40 °C for 3.5 d to afford the product (10.68 g, 23.66 mmol, 56%) as a pale-yellow solid: **^{1}H-NMR** (DMSO-d_6): δ 0.89 (t, $J = 7.2$, 3H), 2.11 (s, 3H), 2.94 (br t, $J = 6.0$, 2H), 3.72 (s, 3H), 3.78 (s, 3H), 3.93 (m, 2H), 3.95 (q, $J = 7.2$, 2H), 6.94 (s, 1H), 6.95 (d, $J = 8.6$, 1H),

7.33 (dd, J = 2.0, 8.6, 1H), 7.58 (d, J = 2.0, 1H), 7.68 (s, 1H), absorptions for the phenol and carboxylic acid moieties were not observed; **EA**: calcd for $C_{25}H_{25}NO_7$: C, 66.51; H, 5.58; N, 3.10. Found: C, 66.25; H, 5.70; N, 3.10; **MS** (HPLC/ES): m/z = 452 (M + 1); **TLC** (silica gel 60, 15% methanol/dichloromethane, UV detection): one spot, R_f = 0.56.

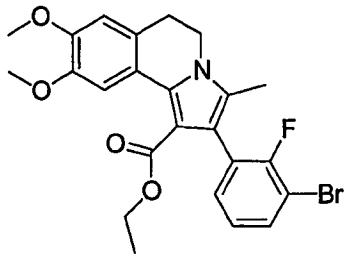
5

3.1. 3-Bromo-2-fluorobenzaldehyde



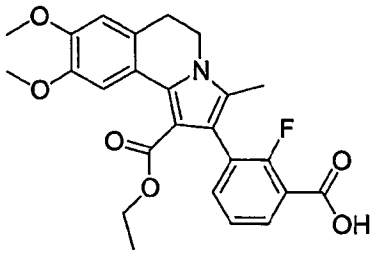
LTMP (lithium tetramethylpiperidine) was prepared by adding butyllithium (37.14 mmol, 14.86 mL) slowly to a solution of 2,2,6,6-tetramethylpiperidine (42.86 mmol, 7.23 mL) in tetrahydrofuran (15 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. This solution was added slowly to a solution of 1,2-bromofluorobenzene (5.0 g, 28.57 mmol, 3.12 mL) in tetrahydrofuran (90 mL) at – 75 °C. The mixture was allowed to stir at this temperature for 2 h, then *N,N*-dimethylformamide (142.86 mmol, 11.05 mL) was added dropwise. After 1 h, the reaction was quenched with water and was concentrated *in vacuo*. The residue was partitioned between ether and water. The aqueous layer was extracted with ether twice and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude residue was dissolved in dichloromethane and passed through a pad of silica eluting with 100:0 to 95:5 hexanes/ethyl acetate to obtain a colorless oil (4.32 g, 70.8 %): **^{1}H-NMR** (DMSO-d_6): δ = 7.34 (m, 1H), 7.82 (m, 1H), 8.03 (m, 1H), 10.15 (s, 1H); **TLC** (10:90 ethyl acetate/hexanes): R_f = 0.70.

3.2. Ethyl 2-(3-bromo-2-fluorophenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



To a mixture of 3-bromo-2-fluorobenzaldehyde (4.2 g, 20.7 mmol, Intermediate 3.1.) was added ethyl 2-(6,7-dimethoxy-2,3,4-trihydro-isoquinolylidene)-acetate (5.76 g, 20.7 mmol, Intermediate 1.2.), nitroethane (41.5 mmol, 2.98 mL) and piperidine (49.8 mmol, 4.93 mL) in 1:1 ratio of isopropanol/ethanol (100 mL) and was heated to 80 °C overnight. The reaction was concentrated *in vacuo* to a minimum volume and treated with methanol (40 mL) until precipitation occurred. The resulting residue was filtered, washed with methanol and concentrated *in vacuo* to give the title compound as a pale pink solid (5.03 g, 49.2 %): **^{1}H-NMR** (CD_2Cl_2): δ = 0.94 (t, J = 5.4, 3H), 2.15 (s, 3H), 3.02 (t, J = 5.0, 2H), 3.89 (s, 6H), 3.98 (t, J = 5.0, 2H), 4.03 (m, 2H), 6.77 (s, 1H), 7.05 (m, 1H), 7.18 (m, 1H), 7.43 (m, 1H), 8.03 (s, 1H).

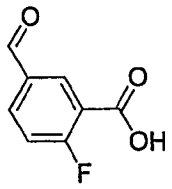
3.3. 3-[1-(Ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-fluorobenzoic acid



A solution of ethyl 2-(3-bromo-2-fluorophenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate (3.00 g, 6.14 mmol, Intermediate 3.2.) in tetrahydrofuran (60 mL) was cooled to – 78 °C and degassed for 5 min. BuLi (9.23 mmol,

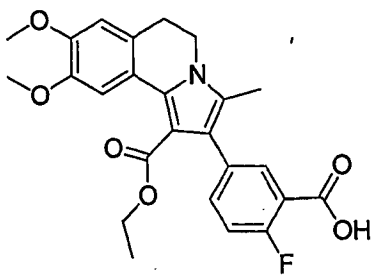
3.69 mL) was added dropwise. The mixture was stirred at – 78 °C for 1 h and CO_2 was bubbled into the solution over a period of 2 h. The reaction was quenched with methanol and concentrated in *vacuo*. The crude residue was purified with 40 M Biotage by eluting with 10:90 methanol/ethyl acetate to obtain desired product as a yellow solid (2.00 g, 71.8 %): **^{1}H-NMR** (CD_2Cl_2): δ = 0.92 (t, *J* = 7.0, 3H), 2.14 (s, 3H), 3.03 (t, *J* = 6.6, 2H), 3.88 (s, 6H), 3.99 (m, 2H), 4.09 (m, 2H), 6.77 (s, 1H), 7.27 (t, *J* = 7.6, 1H), 7.49 (t, 1H), 7.95 (m, 1H), 8.03 (s, 1H).

4.1. 2-Fluoro-5-formyl-benzoic acid



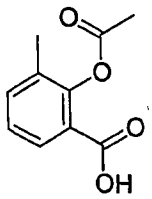
A mixture of 2-fluoro-5-formylbenzonitrile (30.0 g, 201.2 mmol) and concentrated hydrochloric acid (500.0 mL) was heated at reflux under argon for 16 h. Upon cooling to room temperature, a white precipitate was formed. The solid was separated and washed with water (2 X 1500 mL) and dissolved in ethyl acetate (2000 mL). The solution was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to afford 25.8 g of the title compound as a white solid (153.6 mmol, 76.3 %): **^{1}H-NMR** (DMSO-d_6): δ = 7.54 (dd, *J* = 8.5, 10.6, 1H), 8.15 (m, 1H), 8.41 (dd, *J* = 2.4, 7.2, 1H), 10.01 (s, 1H), 13.63 (br s, 1H); **EA**: calcd for $C_8H_5FO_3$: C, 57.15; H, 3.00; F, 11.30. Found: C, 57.00; H, 2.76; F, 11.36.

4.2. 5-[1-(Ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-fluorobenzoic acid



A mixture of 2-fluoro-5-formylbenzoic acid (15.0 g, 89.2 mmol, Intermediate 4.1.), ethyl 2-(6,7-dimethoxy-2,3,4-trihydro-isoquinolylidene)-acetate (12.4 g, 44.6 mmol, Intermediate 1.2.), nitroethane (6.70 g, 89.2 mmol), and piperidine (7.60 g, 89.2 mmol) in a 1:1 mixture of ethanol/isopropanol (500mL) was heated at reflux for 5 h at which time TLC analysis (silica gel 60, 10:90 methanol/dichloromethane, UV detection) suggested complete reaction. The mixture was cooled to 0 °C and washed with concentrated hydrochloric acid (300 mL). The mixture was diluted with water and extracted with dichloromethane (3 X 300 mL). The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was passed through a pad of silica gel eluting with 2:98 methanol/dichloromethane. Further purification by recrysatllization from ethyl acetate/hexanes provided 8.25 g of the title compound as a light yellow solid (18.2 mmol, 40.2 %): **^{1}H-NMR** (DMSO-d_6): δ = 0.86 (t, J = 5.4, 3H), 2.12 (s, 3H), 2.95 (t, J = 4.5, 2H), 3.72 (s, 3H), 3.78 (s, 3H), 3.96 (m, 4H), 6.93 (s, 1H), 7.26 (dd, J = 6.1, 8.0, 1H), 7.42 (m, 1H), 7.60 (dd, J = 1.8, 5.4, 1H), 7.72 (s, 1H); **MS** (HPLC/ES): m/z = 454.0 (M + 1); **LCMS RT** (method A): 3.07 min.

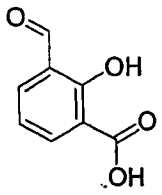
5.1. 2-(Acetyloxy)-3-methylbenzoic acid



To a solution of 3-methylsalicylic acid (20.0 g, 131.5 mmol) in anhydrous pyridine (42.5 mL, 525.8 mmol) was added acetic anhydride (49.6 mL, 525.5 mmol). The reaction was stirred at room temperature under an argon atmosphere for 16 h. The solution was poured

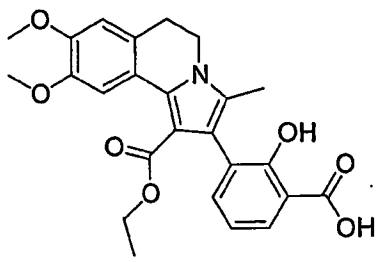
into ice-water and extracted with dichloromethane (3 X 200 mL). The organic extracts were washed with aqueous 1N hydrochloric acid (5 X 80 mL) and brine (2 X 100 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give a white solid (20.67 g, 81 1%): **^{1}H-NMR** (DMSO-d_6): δ 2.16, (s, 1H), 2.27 (s, 3H), 7.25 (t, J = 7.6, 1H), 7.51 (d, J = 7.3, 1H), 7.73 (d, J = 7.7, 1H), 12.95 (s, 1H).

5.2. 3-Formylsalicylic acid



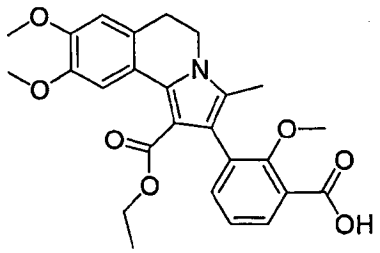
A suspension of 2-(acetyloxy)-3-methylbenzoic acid (13.35 g, 68.8 mmol, Intermediate 5.1.) in carbon tetrachloride (200 mL) was stirred under an argon atmosphere. A 500-watt tungsten lamp was positioned 2 inches directly in front of the reaction. The solution was gently heated with the lamp while a solution of bromine (7.08 mL, 137.5 mmol) in carbon tetrachloride (100 mL) was added dropwise, so that a red color persisted at all times. After the addition was complete, the reaction was allowed to stir an additional 2 h under the light. The reaction was allowed to cool to room temperature and the mixture was washed several times with a saturated aqueous $Na_2S_2O_3$ solution (3 X 150 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography (0:100 to 5:95 methanol/dichloromethane) followed by crystallization (ethyl acetate/hexanes) to give a white solid which was then suspended in 8% aqueous sodium carbonate and stirred, heating to reflux gradually (60° C for 16 h, 85° C for 22 h, reflux 24 h), for 3 d. The mixture was cooled to room temperature and made acidic with the addition of 1N hydrochloric acid. The resulting solid was collected by filtration and dried under high vacuum for 14 h to provide the title compound (7.21 g, 63%): **^{1}H-NMR** (DMSO-d_6): δ 7.05 (t, J = 7.8, 1H), 7.91 (dd, J = 1.8, 7.8, 1H), 8.09 (dd, J = 1.8, 7.7, 1H), 10.35 (s, 1H).

5.3. 3-[1-(Ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-hydroxybenzoic acid



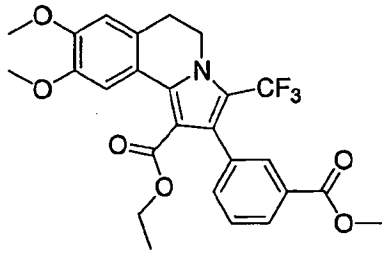
To a solution of ethyl 2-(6,7-dimethoxy-2,3,4-trihydro-isoquinolylidene)-acetate (14.44 g, 52.1 mmol, Intermediate 1.2.) in ethanol (40 mL) was added 3-formylsalicylic acid (7.21 g, 43.4 mmol, Intermediate 5.2.), nitroethane (3.74 mL, 52.1 mmol), and piperidine (5.15 mL, 52.1 mmol). The solution was heated at reflux under an argon atmosphere for 72 h. The reaction was allowed to cool to room temperature and the volatiles were removed *in vacuo*. The crude material was purified by silica gel flash chromatography (eluant 0:100 to 10:90 methanol/dichloromethane) and concentrated *in vacuo* to afford the product as an orange solid (9.7 g, 50 %): **^{1}H-NMR** (DMSO-d_6): δ 0.77 (t, J = 7.0, 3H), 2.07 (s, 3H), 2.98 - 3.03 (m, 2H), 3.71 (s, 3H), 3.78 (s, 3H), 3.86 (q, J = 7.1, 2H), 3.93 (t, J = 6.2, 2H), 6.73 (t, J = 7.5, 1H), 6.92 (s, 1H), 7.13 (d, J = 7.5, 1H), 7.66 (d, J = 7.5, 1H), 7.87 (s, 1H), 8.43 (br s, 1H).

5.4. Ethyl 8,9-dimethoxy-2-[2-methoxy-3-(methoxycarbonyl)phenyl]-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



To a solution of 3-[1-(ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-hydroxybenzoic acid (5.00 g, 11.1 mmol, Intermediate 5.3.) in methyl sulfoxide (70 mL) was added potassium carbonate (9.18 g, 66.4 mmol) and iodomethane (2.76 mL, 44.3 mmol). The solution was stirred at room temperature under an argon atmosphere for 16 h. The reaction mixture was poured into water (150 mL) and was extracted with ethyl acetate (4 X 150 mL). The combined extracts were washed with water (3 X 100 mL), dried over magnesium sulfate and concentrated in vacuo to afford the crude product as an yellow solid, which was purified by trituration with methanol (4.1 g, 77 %): **^{1}H-NMR** (DMSO-d_6) δ 0.74 (t, J = 6.8, 3H), 2.07 (s, 3H), 2.97 (t, J = 6.2, 2H), 3.39 (s, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 3.83 – 3.91 (m, 2H) 3.89 – 4.06 (m, 2H), 6.94 (s, 1H), 7.17 (t, J = 7.5, 1H), 7.29 (dd, J = 1.9, 7.6, 1H), 7.55 (dd, J = 1.8, 7.8, 1H), 7.90 (s, 1H); **MS** (HPLC/ES): m/z = 480.3 (M + 1).

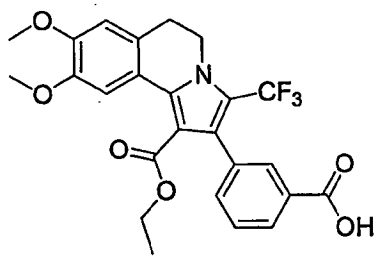
6.0. 3-[1-(Ethoxycarbonyl)-8,9-dimethoxy-3-trifluoromethyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-benzoic acid methyl ester



To a solution of ethyl 2-(6,7-dimethoxy-2,3,4-trihydroisoquinolylidene)acetate (1.13 g, 4.06 mmol Intermediate 1.2.) in 100 mL ethanol was added methyl-3-formylbenzoate (1.00 g, 6.09 mmol), trifluoromethylnitromethane (1.00 mL, 8.12 mmol), and piperidine (600 μL, 6.09 mmol). The resulting solution was heated to 80 °C and was stirred for 18 hours, at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested complete reaction. The crude reaction mixture was concentrated *in vacuo,* and the residue was purified by flash column chromatography eluting with 1:2 ethyl

acetate/hexanes to afford 700 mg (1.39 mmol, 34%) of the title compound: **^{1}H-NMR** (CD_3CN) δ 8.01 (m, 1H), 7.89 (s, 1H), 7.65 (s, 1H), 7.66 (s, 1H), 4.19 (t, J = 6.8 Hz, 2H), 3.98 (q, J = 8.5 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 3.09 (t, J = 8.5 Hz, 2H), 0.85 (t, J = 6.8 Hz, 3H); **MS** (HPLC/ES) m/z = 504.2 (M + 1); **LC RT** (Method G): 3.45 min.

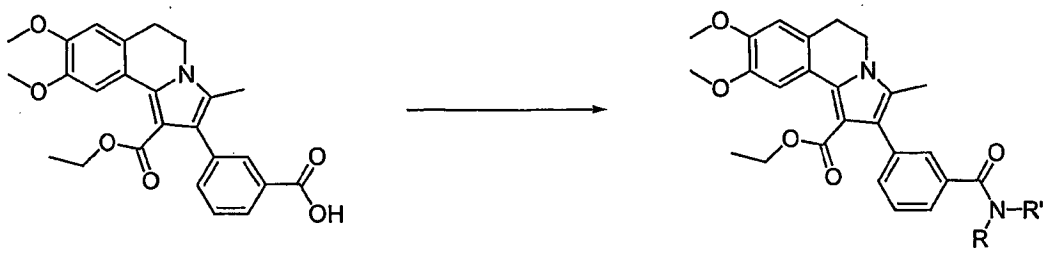
6.1 3-[1-(Ethoxycarbonyl)-8,9-dimethoxy-3-trifluoromethyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-benzoic acid



To a solution of 3-[1-(Ethoxycarbonyl)-8,9-dimethoxy-3-trifluoromethyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-benzoic acid methyl ester (660 mg, 1.31 mmol Intermediate 6.0.) in water/tetrahydrofuran (20 mL, 1:1 vol/vol) was added of lithium hydroxide (628 mg, 26.22 mmol). The resulting solution was heated to 50 °C and was stirred for 18 hours, at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested complete reaction. The crude reaction mixture was concentrated *in vacuo*, and the residue was dissolved in aqueous $NaHCO_3$ (20 mL). The aqueous layer was washed with EtOAc (2 × 20 mL), was made acidic with aqueous 2N hydrochloric acid . The aquesous layer was extracted with dichloromethane/isopropanol (4 × 40 mL, 10:1 vol/vol), and the combined organics were dried ($MgSO_4$), filtered and concentrated to afford the title compound (344 mg, 0.704 mmol, 54%): **^{1}H-NMR** (DMSO, d^6) δ 13.01 (br. s., 1H), 7.92 (dt, J = 7.0, 1.5 Hz, 1H), 7.76 (s, 1H), 7.59 (s, 1H), 7.49 (m, 2H), 7.02 (s, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.90 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.07 (t, J = 7.1 Hz, 2H), 0.75 (t, J = 7.1 Hz, 3H); **MS** (HPLC/ES) m/z = 490.2 (M + 1); **LC RT** (Method G): 2.92 min.

Amine Coupling Procedures

Method A: Parallel Synthesis Method

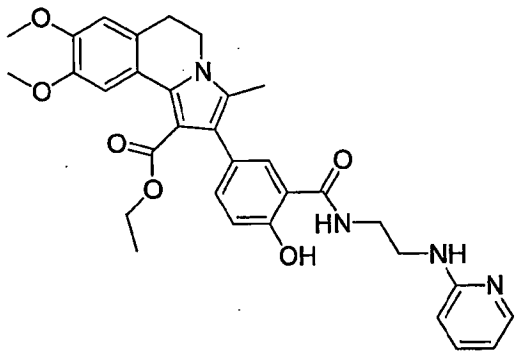


The amines used in this experiment were prepared as 0.5 M solution in dichloromethane by using Bohdan weight station. The amine solutions (270µl, 135.0 µmol) were dispensed into 96-well format FlexChem® Multiple Synthesis Reactor Block by using Tecan station. Ethyl 2-(3-carboxyphenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate (60mg/1ml DCM, 137.8 µmol, Intermediate 1.3.) was added to each well by Bohdan dispense station. PS-DCC resin (n-cyclohexylcarbodiimide, n'-methyl polystyrene HL, 1.9 mmol/g, 140 mg, 266 µmol) was then loaded to each well of the 96-well format FlexChem® Multiple Synthesis Reactor Block. The block was then sealed and stirred by rotation motion in a FlexChem® Rotating Oven at ambient temperature for 12 h. The solution in each well was released to 96 deep well plate. The resin was washed with dichloromethane (3 X 2 ml) and the dichloromethane was released to the other deep well plates. After concentration to remove solvents, the combined material was diluted with dichloromethane and transferred to 96-well format FlexChem® Multiple Synthesis Reactor Block. PS-Isocynate (80 mg, 100µmol, 1.7 mmol/g) was loaded to each of well which contains the reaction mixture. The block was then sealed and stirred by rotation motion in a FlexChem® Rotating Oven at ambient temperature for 12 h to scavenge the excess amine. The resin was filtered and washed with dichlormethane (3 X 2ml). The dichloromethane solution was collected into a 96 deep well plate. The solution was then transferred by Tecan to 80 individual pre-weighed 8 ml vials. The

solvent was removed in vacuo and the product was weighed with a Bohdan weight station. Products were confirmed by both ^{1}HNMR and LC-MS.

Method B

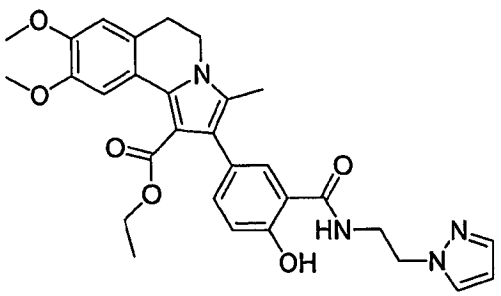
Example 1: Ethyl 2-[4-hydroxy-3-({[2-(2 pyridinylamino)ethyl]amino} carbonyl)-phenyl]-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



A mixture of 5-[1-(ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-hydroxybenzoic acid (100 mg, 0.230 mmol, Intermediate 2.1.), N-(2-aminoethyl)-N-(2-pyridinyl)-amine (63.0 mg, 0.46 mmol), PS-DCC (N-cyclohexylcarbodiimide, N'-methyl polystyrene HL, 117 mg, 0.344 mmol), and 1-hydroxybenzotriazole (62.0 mg, 0.46 mmol) in tetrahydrofuran (1 mL) and dichloromethane (2 mL) was reacted at room temperature for 18 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. Purification by silica gel flash chromatography provided ethyl 2-[4-hydroxy-3-({[2-(2-pyridinylamino)ethyl]-amino}carbonyl)phenyl]-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate (135 mg, 71%): **MS** (HPLC/ES): m/z = 571.0 (M + 1; **LCMS RT** (method A): 2.49 min.

Method C

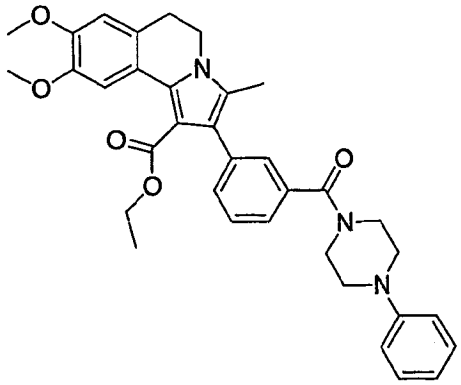
Example 2: Ethyl 2-[4-hydroxy-3-({[2-(1H-pyrazol-1-yl)-ethyl]-amino}-carbonyl)-phenyl]-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]-isoquinoline-1-carboxylate



To a solution of 70 mg (0.16 mmol) of 5-[1-(ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-hydroxybenzoic acid (Intermediate 2.1.) in 5 mL of tetrahydrofuran was added 45 mg (0.23 mmol) of EDCI, 31 mg (0.23 mmol) of 1-hydroxybenzotriazole, and 60 μL of triethylamine. After 30 min on the J-Kem block, 45 mg (0.23 mmol) of 2-(1H-pyrazol-1-yl)ethylamine was added. This was allowed to shake for 18 h, at which time TLC analysis (silica gel 60, 90:10 dichloromethane/methanol, UV detection) suggested complete reaction. The reaction mixture was concentrated in vacuo and the crude product was purified by preparative HPLC, which afforded 35 mg (0.064 mmol, 41%) of product as a pink solid: **^{1}H-NMR** (CD_3CN) δ 0.95 (t, J = 7.0, 3H), 2.16 (s, 3H), 3.01 (t, J = 6.4, 2H), 3.77 (m, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 3.98 (m, 2H), 4.03 (q, J = 7.2, 2H), 4.36 (t, J = 5.7, 2H), 6.24 (t, J = 1.9, 1H), 6.92 (m, 2H), 7.28 (dd, J = 2.2, 8.6, 1H), 7.37 (d, J = 2.3, 1H), 7.47 (m, 1H), 7.53 (m, 1H), 7.63 (br s, 1H), 7.79 (s, 1H) 12.5 (s, 1H); **MS** (HPLC/ES) m/z = 545.0 (M + 1); **LCMS RT** (method B) 3.14 min.

Method D

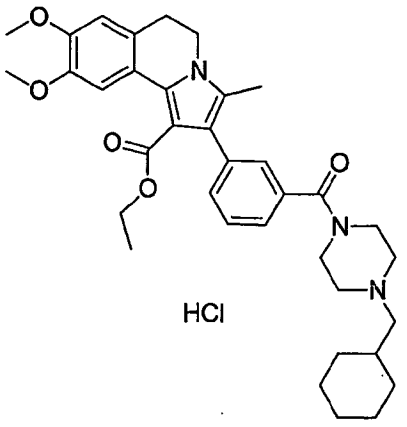
Example 3: Ethyl 8,9-dimethoxy-3-methyl-2-{3-[(4-phenyl-1-piperazinyl)-carbonyl]-phenyl}-5,6-dihydropyrrolo[2,1-a]-isoquinoline-1-carboxylate



To a solution of 500 mg (1.148 mmol) of 3-[1-(ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]benzoic acid (Intermediate 1.3.) in 10 mL of dichloromethane was added 279 μL (1.72 mmol) of 1-phenylpiperazine, followed by 160 μL (148 mmol) triethylamine, 242 mg (1.26 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and 14 mg (0.115 mmol) of 4-dimethylaminopyridine. The resultant clear yellow solution was stirred at room temperature under an argon atmosphere for 16 h, at which time TLC analysis (silica gel 60, 2:3 ethyl acetate/hexanes, UV detection) suggested complete reaction. The organics were washed with 1 N hydrochloric acid (1 X 25 mL) and saturated aqueous $NaHCO_3$ solution (1 X 25 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was recrystallized from ether:hexanes to provide 189.1 mg (0.326 mmol, 28%) of a cystalline solid: **^{1}H-NMR** ($CDCl_3$): δ = 0.95 (t, J = 7.1, 3H), 2.17 (s, 3H), 3.00 (t, J = 6.0, 2H), 3.20 (m, 4H), 3.67 (m, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 4.04 (q, J = 7.0, 2H), 6.73 (s, 3H), 6.92 (m, 3H), 7.30 (m, 5H), 7.93 (s, 1H); **MS** (HPLC/ES): m/z = 580.9 (M + 1); **LCMS RT** (method A): 3.41 min; **TLC** (30:70 ethyl acetate/hexanes): R_f = 0.31.

Method E

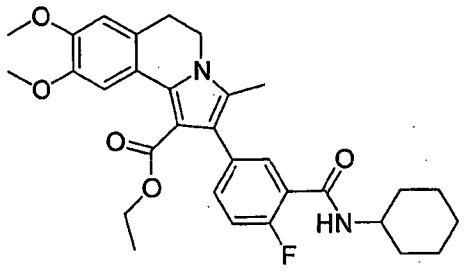
Example 4: Ethyl 2-(3-{[4-(cyclohexylmethyl)-1-piperazinyl]-carbonyl}-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]-isoquinoline-1-carboxylate hydrochloride



To a solution of 3-[1-(ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]-isoquinolin-2-yl]-benzoic acid (871 mg, 2 mmol, Intermediate 1.3.) in dichloromethane (10 mL) was added 1-hydroxybenzotriazole (270 mg, 2 mmol) and 4-methylmorpholine (0.66 mL, 6 mmol). The reaction mixture was cooled to –10° C, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (383 mg, 2.0 mmol) was added. After being stirred for 10 min, the mixture was allowed to warm to room temperature for 20 min, and was subsequently cooled to –10°C. To the cooled reaction mixture was added 1-cyclohexylmethylpiperazine (438 mg, 2.4 mmol). The solution was allowed to warm to room temperature, and was stirred for 16 h. Subsequently, aqueous 1N $KHSO_4$ solution (5 mL) was added, and the two phases were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified with a Biotage Quad 4 system (25 M column) eluting with 50:50 ethyl acetate/hexanes to afford the free base as a solid. The solid was treated with hydrochloric acid (1M in ether, 2 mL). The resultant precipitate was recovered by filtration and was dried in a vacuum oven to afford the title compound (760 mg, 60%): **MS** (HPLC/ES): m/z = 600.2 (M + 1); **LCMS RT** (method A): 2.57 min.

Method F

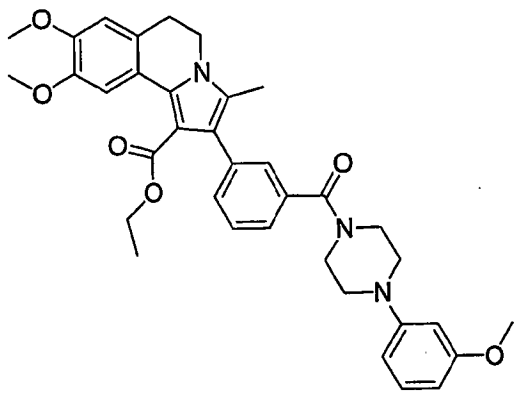
Example 5: Ethyl-2-{3-[(cyclohexylamino)-carbonyl]-4-fluorophenyl}-8,9-dimethoxy-3-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate



To a 0 °C solution of 100 mg (0.22 mmol) of 5-[1-(ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]-2-fluorobenzoic acid (Intermediate 4.2.) in 4 mL of tetrahydrofuran was added 20 µL (0.26 mmol) of oxalyl chloride dropwise followed by one drop of *N,N*-dimethylformamide. This was warmed to room temperature and was stirred for 1.5 h. The resulting solution was concentrated *in vacuo* and the oil was diluted with 4 mL of tetrahydrofuran, followed by the addition of 60 µL (0.44 mmol) of triethylamine and 40 µL (0.33 mmol) of cyclohexylamine. This was stirred for 1 h, at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested complete reaction. The reaction mixture was diluted with water and ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 X 10 mL), and the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by preparative TLC eluting with 50:50 ethyl acetate/hexanes which afforded 23.2 mg (0.043 mmol, 20%) of the title compound as an off-white solid: **MP** 140-142 °C; **^{1}H-NMR** (CD_3CN) δ 0.99 (t, J = 7.5, 3H), 1.39 (m, 2H), 1.67 (br s, 1H), 1.79 (br s, 2H), 2.17 (s, 3H), 3.00 (t, J = 7.0, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 3.97 (t, J = 6.3, 2H), 4.07 (m, 2H), 6.83 (br s, 1H), 6.90 (s, 1H), 7.18 (m, 1H), 7.34 (m, 1H), 7.60 (dd, J = 2.3, 6.9, 1H), 7.73 (s, 1H); **MS** (HPLC/ES) 535.2 m/z = (M + 1); **LCMS RT** (method B): 3.53 min.

Method G

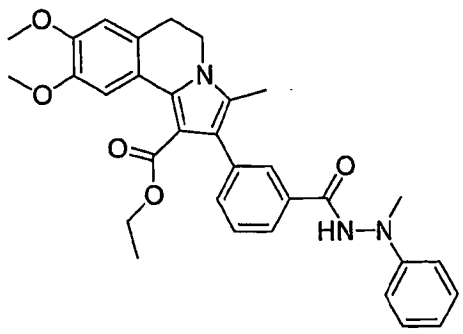
Example 6: Ethyl-8,9-dimethoxy-2-(3-{[4-(3-methoxyphenyl)-1-piperazinyl]}-phenyl)-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



To a solution of 150 mg (0.345 mmol) of 3-[1-(ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-2-yl]benzoic acid (Intermediate 1.3.) in 4 mL tetrahydrofuran was added 0.08 mL (0.448 mmol) of *N,N*-diisopropylethyl amine. After 5 min 233 mg (0.448) of PyBop and 86.0 mg (0.448 mmol) of 1-(3-methoxyphenyl)piperazine were added. The resulting mixture was stirred for 18 h at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested complete reaction. The reaction mixture was diluted with water, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by preparative TLC eluting with 50:50 ethyl acetate/hexanes to afford 140 mg (0.23 mmol, 67%) of the title compound: **MP**: 97-99 °C; **^{1}H-NMR** ($CDCl_3$) δ 0.94 (t, J = 7.6, 3H), 2.17 (s, 3H), 3.00 (t, J = 6.4, 2H), 3.19 (m, 4H), 3.79 (s, 3H), 3.92 (m, 12H), 4.04 (q, J = 7.6, 2H), 6.46 (m, 2H), 6.54 (d, J = 7.1, 1H), 6.72 (s, 1H), 7.18 (t, J = 8.5, 1H), 7.37 (m, 4H), 7.93 (s, 1H); **MS** (HPLC/ES) m/z = 610.4 (M + 1); **LCMS RT** (method B) 3.25 min.

Method H

Example 7: Ethyl 8,9-dimethoxy-3-methyl-2-{3-[(2-methyl-2-phenylhydrazino)-carbonyl]-phenyl}-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate

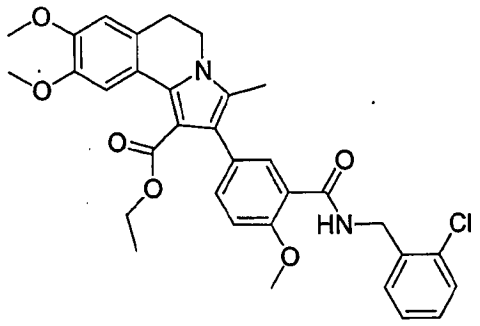


3-[1-(Ethoxycarbonyl)-8,9-dimethoxy-3-methyl-5, 6-dihydropyrrol[2,1-a] isoquinolin -2-yl] benzoic acid (100 mg, 0.23 mmol, Intermediate 1.3.), 1-methyl-1-phenylhydrazine (56.1 mg, 0.46 mmol), PS-DCC (n-cyclohexylcarbodiimide, n'-methyl polystyrene HL, 340 mg, 0.35 mmol) and 1-hydroxybenzotriazole (62.06 mg, 0.46 mmol) were dissolved in dry dichloromethane (1.5 mL) and tetrahydrofuran (1.5 mL) and was stirred overnight. The resin was filtered off and the solvent was removed in vacuo. The residue was purified by Biotage using 50:50 ethyl acetate/hexanes to give 103.9 mg (83.9 %) of the title compound: **MS** (HPLC/ES): m/z = 540.2 (M + 1); **LCMS RT** (method A): 3.27 min; **TLC** (50:50 ethyl acetate/hexanes): $R_f = 0.22$.

General Procedures

Method I

Example 8: Ethyl 2-(3-{[(2-chlorobenzyl)-amino]-carbonyl}-4-methoxyphenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



To a solution of 99.8 mg (0.17 mmol) of ethyl 2-(3-{[(2-chlorobenzyl)-amino]-carbonyl}-4-hydroxyphenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate was added 25 mg (1.04 mmol) of potassium carbonate and 40 μL (0.69 mmol) of iodomethane. The reaction was heated to 80 °C for 18 h, at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested complete reaction. The reaction contents were diluted with water and ethyl acetate and the layers were separated. The organic layer was washed with water (3 X 5 mL), dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by preparative TLC eluting with 50:50 ethyl acetate/hexanes to afford 32.0 mg (0.054 mmol, 31%) of the title compound as a yellowish solid: **^{1}H-NMR** (CD_3CN) δ 0.98 (t, J = 6.8, 3H), 2.19 (s, 3H), 2.99 (t, J = 6.4, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 3.95 (t, J = 6.4, 2H), 4.02 (s, 3H), 4.06 (m, 2H), 4.69 (d, J = 5.5, 2H), 6.89 (s, 1H), 7.15 (d, J = 8.3, 1H), 7.33 (m, 3H), 7.44 (m, 2H), 7.68 (s, 1H), 7.87 (d, J = 2.3, 1H), 8.53 (t, J = 4.2, 1H); **MS** (HPLC/ES) m/z = 589.4 (M + 1); **LCMS RT** (method B) 3.81 min.

Method J

1. Formation of solid phase bound propylamine:

4-(4-Formyl-3-methoxyphenoxy)-butyryl aminomethyl resin (NovaBiochem; 10.0 g, 0.78 mmol/g) is suspended in dichloromethane (80 ml)/trimethyl orthoformiate (40 ml).

Propylamine (2.31 g, 5 equiv.) is added and the reaction mixture is shaken at room temperature overnight. The mixture is filtered and the resin is washed twice with dimethylformamide. The resin is re-suspended in dimethylformamide (100 ml), and tetrabutylammonium borohydride (4.01 g, 2 equiv.) is added to the mixture. After shaking for 15 min at room temperature, the mixture is cooled to – 40 °C, a solution of acetic acid (44 ml)/dimethylformamide (20 ml) is added, and the reaction mixture is warmed to room temperature again and shaken for an additional 30 min. The resin is filtered and repeatedly washed with dimethylformamide, dimethylformamide/N,N-diisopropyl ethylamine (9:1), dimethylformamide, methanol, dichloromethane and diethyl ether, and dried *in vacuo*.

2. Acylation of propylamine on solid phase:

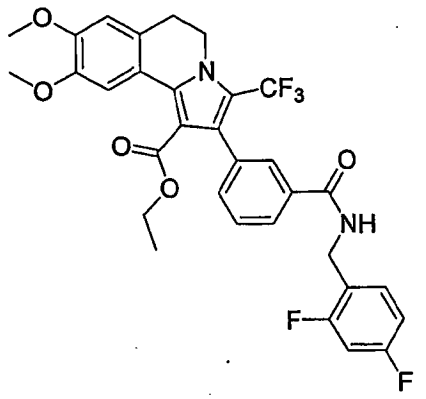
The propylamine resin from above (3.00 g, 2.34 mmol) is suspended in dichloromethane (30 ml). N,N-diisopropyl ethylamine (1.81 g, 6 equiv.) is added with stirring, followed by 3-formylbenzoic acid chloride (1.18 g, 3 equiv.). The mixture is shaken for 1 h at room temperature. The resin is filtered and repeatedly washed with methanol, dimethylformamide, methanol, dichloromethane and diethyl ether, and dried *in vacuo*.

3. Formation of heterocycle:

The formylbenzoic acid amide resin from above (1.00 g, 0.78 mmol) is suspended in dioxane (6 ml)/isopropanol (3 ml). The respective nitroalkane (5 equiv.) and ammonium acetate (300 mg, 5 equiv.) are added, and the mixture is shaken at 100 °C overnight. The resin is filtered, repeatedly washed (methanol, water, dimethylformamide, methanol, dichloromethane and diethyl ether), and dried *in vacuo*. The resin is re-suspended in dioxane (6 ml)/ethanol (3 ml), Intermediate 1.2 (432 mg, 2 equiv.) is added, and the mixture is shaken at 80 °C overnight. The resin is filtered, repeatedly washed (methanol, dichloromethane, diethyl ether) and dried *in vacuo*. The crude product is cleaved from solid phase with 50% trifluoroacetic acid in dichloromethane.

Method K

Example: 9: Ethyl 2-(3-{[(2,4-difluorobenzyl)-amino]-carbonyl}-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate

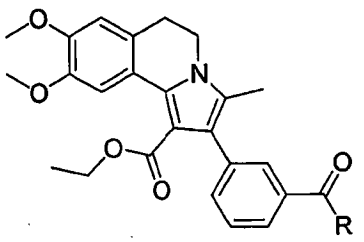


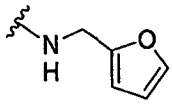
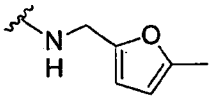
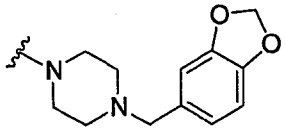
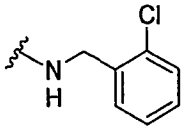
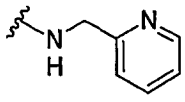
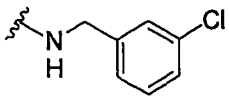
To a solution of of ethyl 2-(6,7-dimethoxy-2,3,4-trihydroisoquinolylidene)acetate (100 mg, 0.36 mmol, Intermediate 1.2.) in ethanol (5 mL) was 3-formyl-N-(2,4-difluorobenzyl)-benzamide (149 mg, 0.54 mmol), trifluoromethylnitromethane (90 μL, 0.72 mmol), and piperidine (50 μL, 0.54 mmol). The resulting solution was heated to 80 °C and was stirred for 18 hours, at which time TLC analysis (silica gel 60, 50:50 ethyl acetate/hexanes, UV detection) suggested complete reaction. The crude reaction mixture was concentrated *in vacuo* and the resulting crude solid was purified by preparative HPLC eluting with 10-90% acetonitrile/water over 3.5 minutes to afford the title compound as a white solid (24.8 mg, 0.040 mmol, 11%): **^{1}H-NMR** (CD_3CN) δ 7.82 (dt, J = 7.4, 1.6 Hz, 1H), 7.73 (m, 1H), 7.66 (s, 1H), 7.56 (m, 1H), 7.46 (m, 3H), 6.96 (m, 3H), 4.57 (d, J = 5.8 Hz, 2H), 4.19 (t, J = 6.2 Hz, 2H), 3.97 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.81 (m, 3H), 3.09 (t, J = 6.8 Hz, 2H) 0.82 (t, J = 7.2 Hz, 3H); **MS** (HPLC/ES) m/z = 615.1 (M + 1); **HPLC RT** (Method G): 3.37 min.

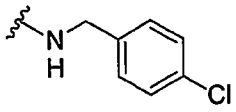
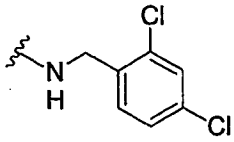
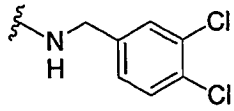
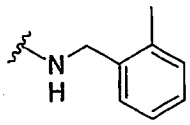
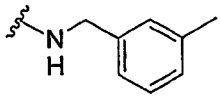
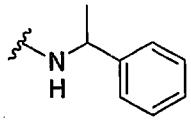
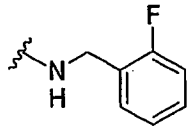
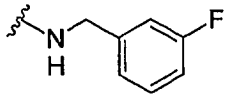
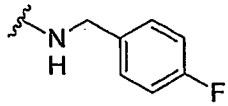
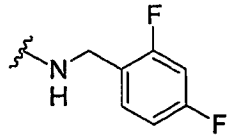
Preparation Examples

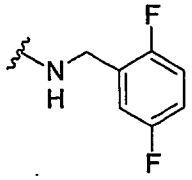
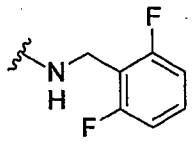
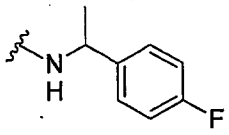
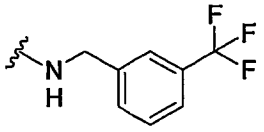
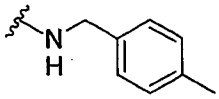
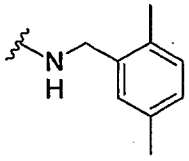
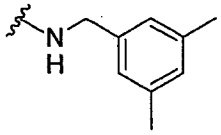
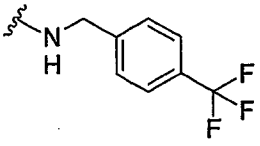
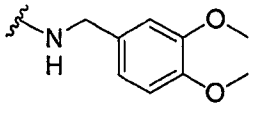
Table 1

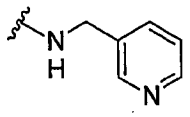
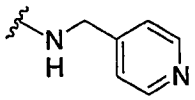
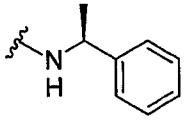
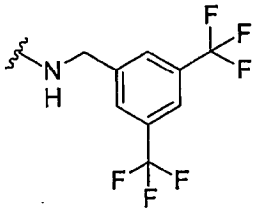
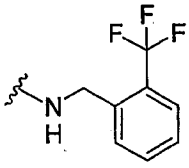
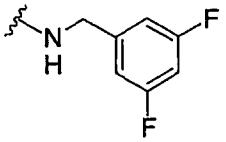
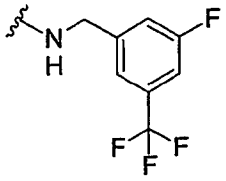
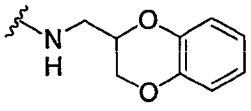
The following amides were prepared from Intermediate 1.3. using the amine coupling procedure indicated.

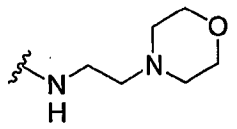
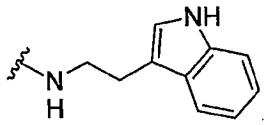
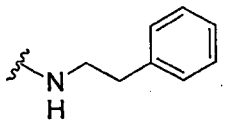
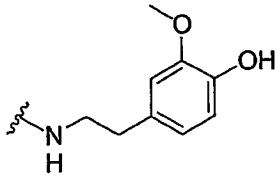
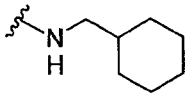
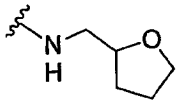
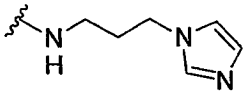
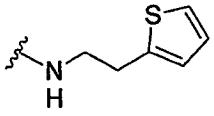
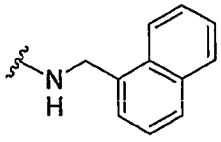
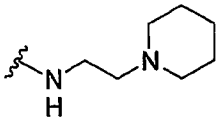


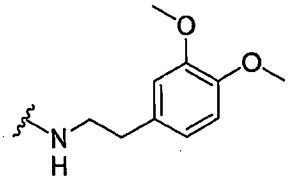
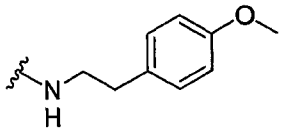
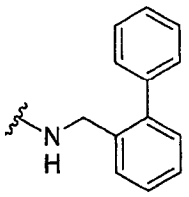
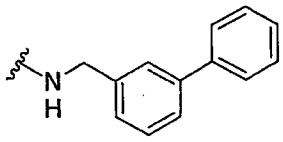
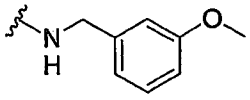
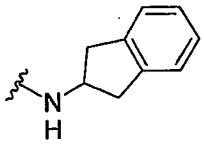
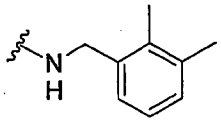
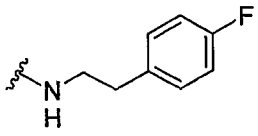
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
10		515.4	2.92	B	A
11		529.5	3.15	B	A
12		638.5	2.31	B	A
13		559.4	3.33	B	A
14		542.4	2.34	B	A
15		559.4	3.29	B	A

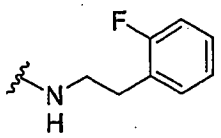
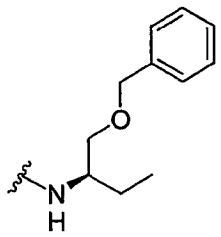
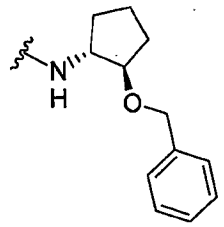
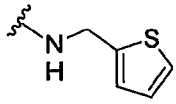
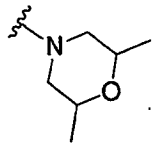
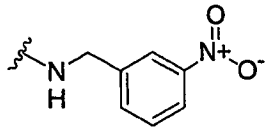
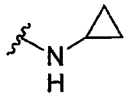
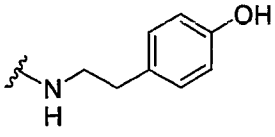
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
16		559.4	3.25	B	A
17		593.4	3.44	B	A
18		593.4	3.41	B	A
19		539.5	3.16	B	A
20		539.5	3.19	B	A
21		539.5	3.20	B	A
22		543.4	3.09	B	A
23		543.4	3.14	B	A
24		543.4	3.13	B	A
25		561.4	3.19	B	A

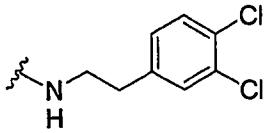
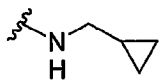
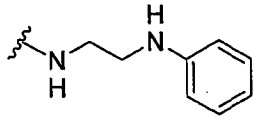
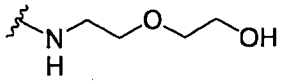
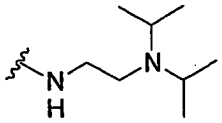
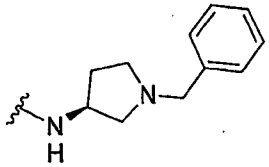
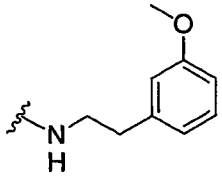
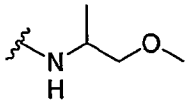
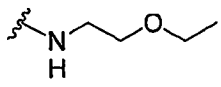
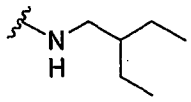
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
26		561.4	3.16	B	A
27		561.4	3.10	B	A
28		557.5	3.24	B	A
29		593.4	3.33	B	A
30		539.5	3.24	B	A
31		553.5	3.35	B	A
32		553.5	3.31	B	A
33		593.4	3.33	B	A
34		585.5	2.92	B	A

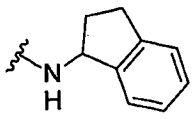
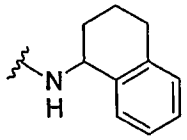
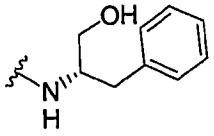
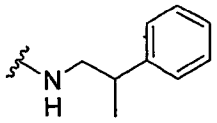
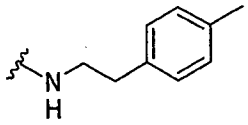
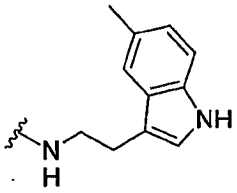
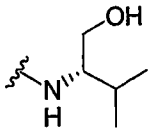
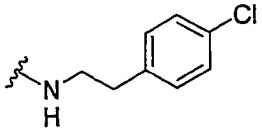
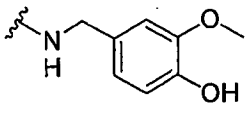
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
35		526.4	2.10	B	A
36		526.4	2.09	B	A
37		539.5	3.16	B	A
38		661.4	3.58	B	A
39		593.4	3.31	B	A
40		561.4	3.19	B	A
41		611.4	3.39	B	A
42		583.5	3.18	B	A

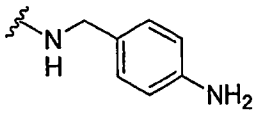
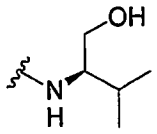
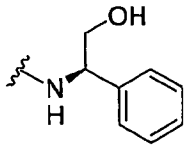
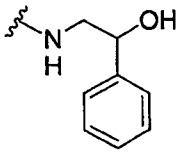
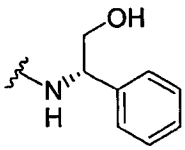
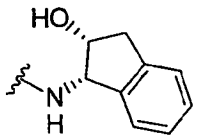
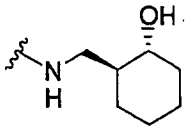
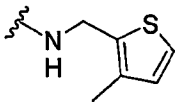
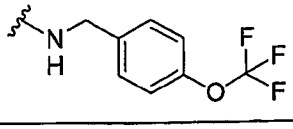
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
43		548.5	2.07	B	A
44		578.5	3.09	B	A
45		539.5	3.14	B	A
46		585.5	2.80	B	A
47		531.5	3.32	B	A
48		519.4	2.73	B	A
49		543.5	2.08	B	A
50		545.4	3.08	B	A
51		575.5	3.34	B	A
52		546.5	2.16	B	A

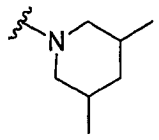
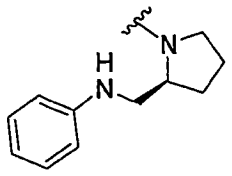
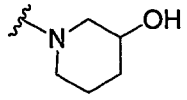
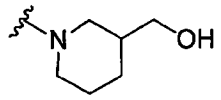
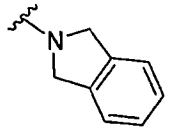
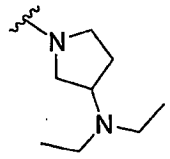
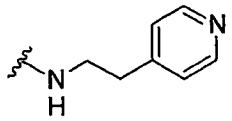
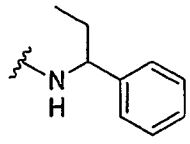
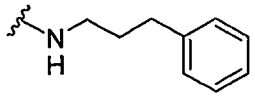
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
53		599.5	2.94	B	A
54		569.5	3.09	B	A
55		601.5	3.46	B	A
56		601.5	3.49	B	A
57		555.5	3.05	B	A
58		551.5	3.23	B	A
59		553.5	3.34	B	A
60		557.5	3.17	B	A

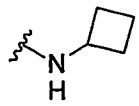
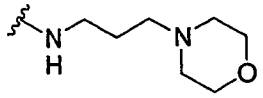
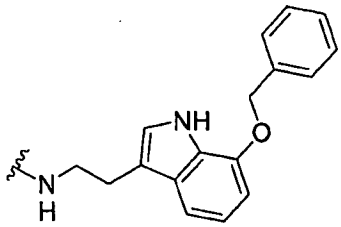
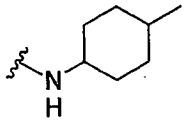
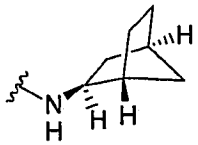
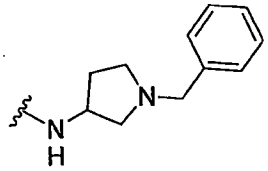
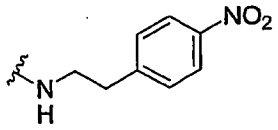
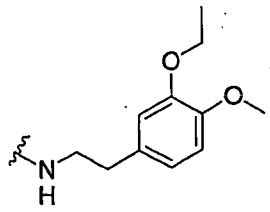
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
61		557.5	3.18	B	A
62		597.5	3.33	B	A
63		609.5	3.34	B	A
64		531.4	3.04	B	A
65		533.5	2.87	B	A
66		570.4	3.14	B	A
67		475.4	2.75	B	A
68		555.5	2.95	B	A

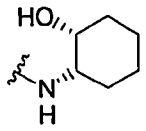
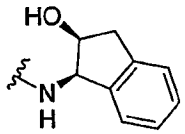
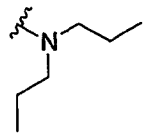
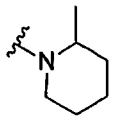
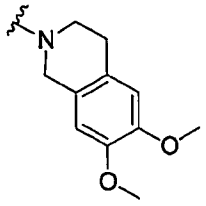
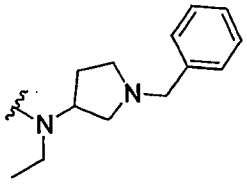
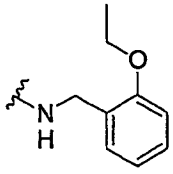
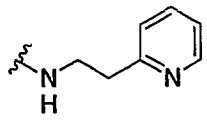
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
69		607.4	3.48	B	A
70		489.5	2.97	B	A
71		554.5	2.77	B	A
72		523.5	2.51	B	A
73		562.5	2.25	B	A
74		594.5	2.33	B	A
75		569.5	3.09	B	A
76		507.4	2.74	B	A
77		507.5	2.81	B	A
78		519.5	3.37	B	A

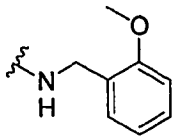
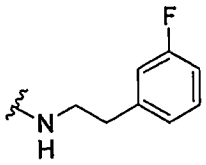
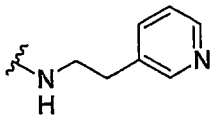
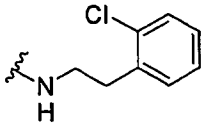
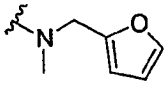
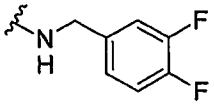
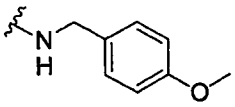
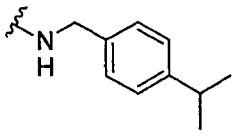
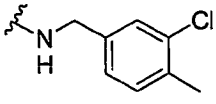
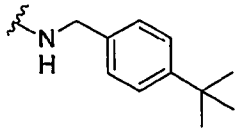
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
79		551.3	3.34	B	A
80		565.5	3.44	B	A
81		569.5	2.87	B	A
82		553.5	3.34	B	A
83		553.5	3.32	B	A
84		592.5	3.27	B	A
85		521.5	2.70	B	A
86		573.2	3.39	B	A
87		571.5	2.81	B	A

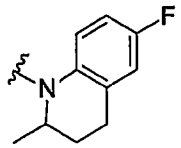
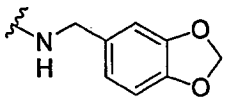
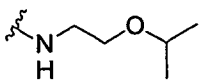
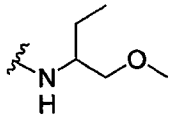
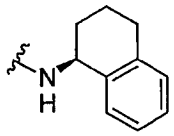
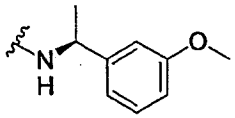
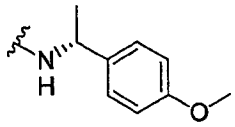
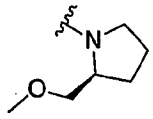
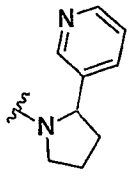
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
88		540.5	2.26	B	A
89		521.5	2.73	B	A
90		555.5	2.89	B	A
91		555.5	2.92	B	A
92		555.5	2.87	B	A
93		567.5	2.99	B	A
94		547.5	2.84	B	A
95		545.4	3.24	B	A
96		609.4	3.45	B	A

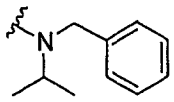
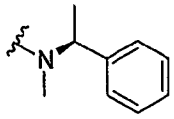
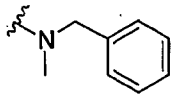
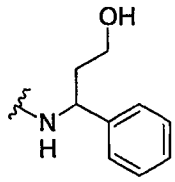
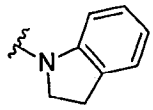
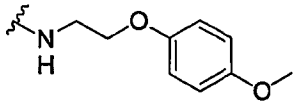
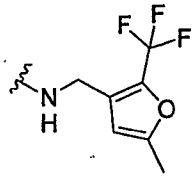
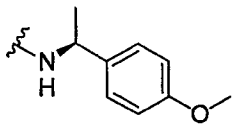
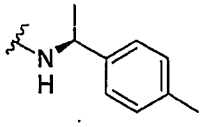
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
97		531.5	3.36	B	A
98		594.5	3.06	B	A
99		519.5	2.59	B	A
100		533.5	2.63	B	A
101		537.5	3.00	B	A
102		560.5	2.15	B	A
103		540.5	2.27	B	A
104		553.5	3.40	B	A
105		553.4	3.28	B	A

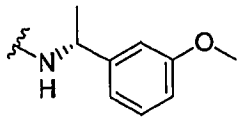
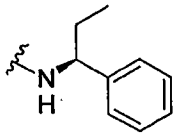
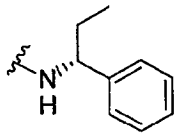
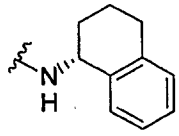
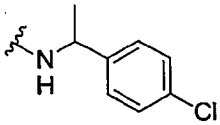
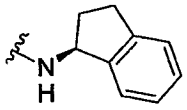
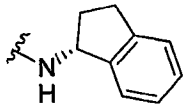
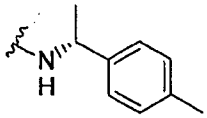
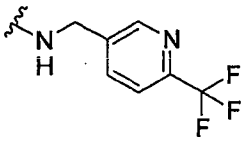
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
106		489.4	3.06	B	A
107		562.5	2.23	B	A
108		687.5	3.65	B	A
109		531.4	3.41	B	A
110		529.4	3.32	B	A
111		594.5	2.37	B	A
112		584.5	3.16	B	A
113		613.5	3.24	B	A

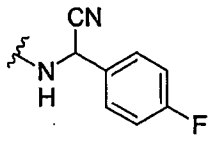
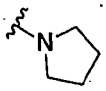
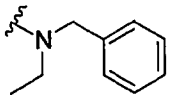
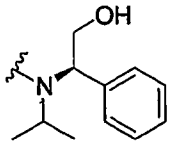
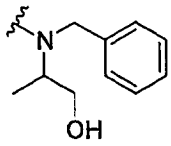
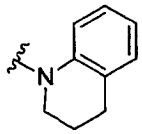
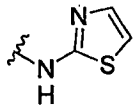
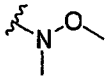
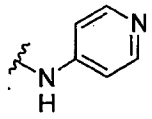
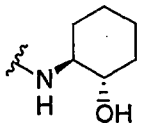
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
114				B	A
115		567.5	3.03	B	A
116		519.5	3.43	B	A
117		517.4	3.14	B	A
118		611.5	3.10	B	A
119		622.5	2.58	B	A
120		569.5	3.33	B	A
121		540.5	2.38	B	A

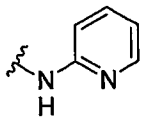
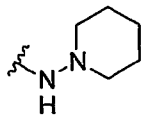
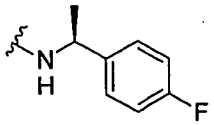
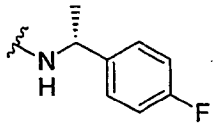
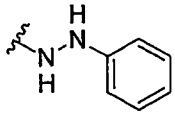
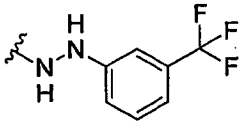
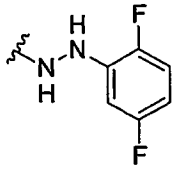
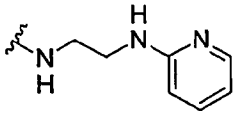
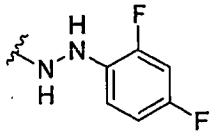
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
122		555.5	3.30	B	A
123		557.5	3.29	B	A
124		540.5	2.30	B	A
125		573.4	3.40	B	A
126		529.4	3.13	B	A
127		561.4	3.31	B	A
128		555.5	3.14	B	A
129		567.5	3.49	B	A
130		573.4	3.52	B	A
131		581.5	3.72	B	A

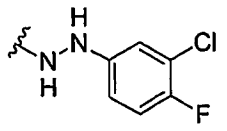
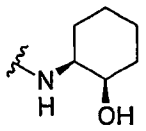
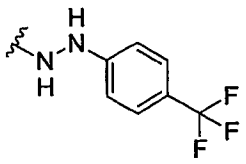
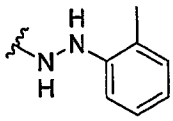
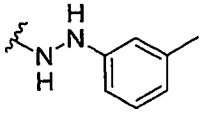
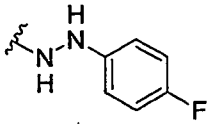
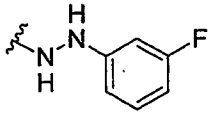
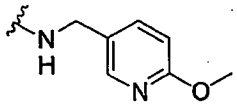
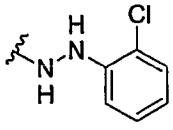
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
132		583.6	3.64	B	A
133		569.2	3.01	B	A
134		521.3	2.77	B	A
135		521.3	2.82	B	A
136		565.3	3.30	B	A
137		569.3	3.12	B	A
138		569.3	3.10	B	A
139		533.3	2.71	B	A
140		566.3	2.18	B	A

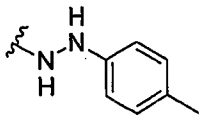
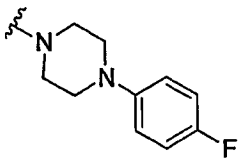
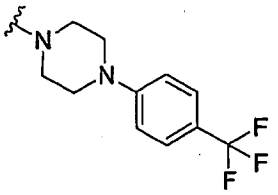
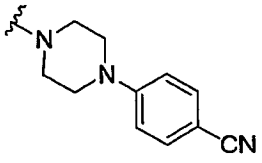
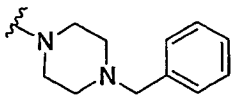
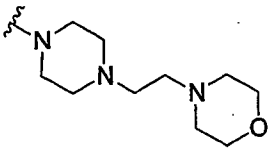
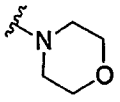
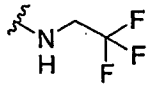
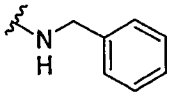
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
141		567.3	3.26	B	A
142		553.3	3.19	B	A
143		539.2	3.08	B	A
144		569.3	2.73	B	A
145		537.2	3.19	B	A
146		585.3	3.40	B	A
147		597.2	3.60	B	A
148		569.3	3.49	B	A
148		553.3	3.64	B	A

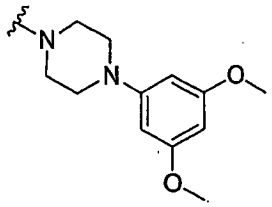
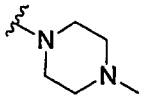
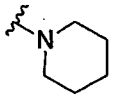
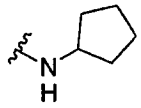
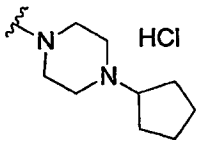
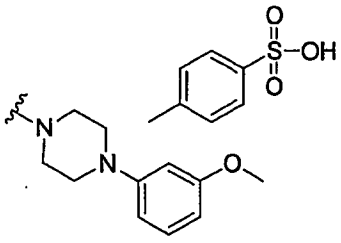
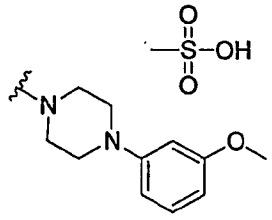
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
150		569.3	3.50	B	A
151		553.3	3.63	B	A
152		553.3	3.56	B	A
153		565.3	3.60	B	A
154		573.2	3.67	B	A
155		551.2	3.20	B	A
156		551.2	3.61	B	A
157		553.3	3.57	B	A
158		594.2	3.49	B	A

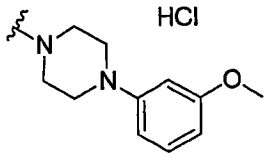
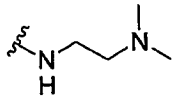
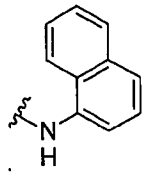
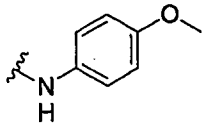
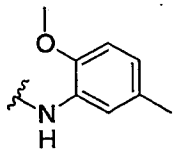
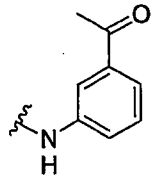
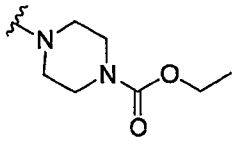
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
159		568.2	3.49	B	A
160		489.2	2.94	B	A
161		553.3	3.64	B	A
162		597.3	2.83	B	A
163		583.3	3.27	B	A
164		551.2	3.47	B	A
165		518.0	3.15	A	F
166		479.0	3.07	A	C
167		512.0	2.56	A	F
168		533.3	2.96	A	F

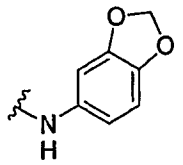
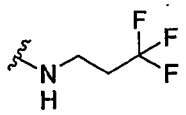
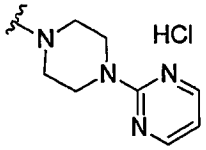
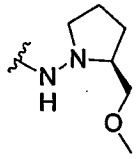
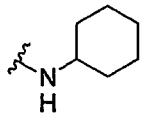
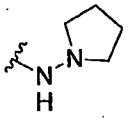
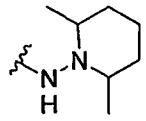
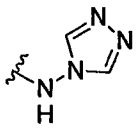
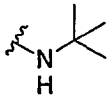
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
169		512.0	2.86	A	Fa
170		518.0	2.74	A	H
171		556.1	3.46	B	C
172		556.1	3.51	B	C
173		525.9	3.21	A	H
174		594.0	3.54	A	H
175		562.2	3.32	A	H
176		555.0	2.42	A	B
177		562.0	3.38	A	H

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
178		577.9	3.45	A	H
179		533.2	2.98	A	B
180		594.0	3.52	A	H
181		540.3	3.25	A	H
182		540.3	3.25	A	H
183		544.2	3.18	A	H
184		544.3	3.18	A	H
185		555.9	3.04	A	B
186		559.9	3.52	A	H

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
187		539.9	3.42	A	H
188		598.6	3.49	B	G
189		648.5	3.78	B	G
190		604.6	3.37	B	G
191		594.4	2.55	B	G
192		617.5	2.33	B	G
193		505.1	2.85	A	E
194		516.9	3.28	A	E
195		524.9	3.38	A	D

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
196		640.4	3.26	A	G
197		462.9	2.94	A	G
198		518.0	2.08	A	G
199		502.9	3.26	A	D
200		503.0	3.35	A	G
201		572.2	2.39	A	G
202		610.0	3.41	A	C
203		610.0	3.41	A	C

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
204		610.0	3.41	A	C
205		506	4.13	C	G
206		449	4.26	C	G
207		561	3.16	C	G
208		541	1.87	E	G
209		555	5.03	F	G
210		551 $(M-H)^+$	4.49	F	G
211		593	4.67	C	G

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
212		553 $(M-H)^+$	4.51	F	G
213		529 $(M-H)^+$	4.39	F	G
214		582	2.67	E	G
215		548.1	1.98	F	C
216		517.4	3.13	F	C
217		504	2.44	A	H
218		546.2	3.13	A	C
219		502.9	2.26	A	C
220		506.4	2.17	F	C

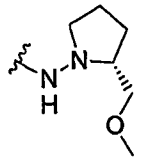
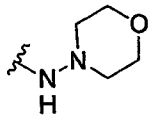
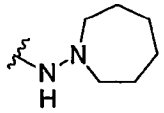
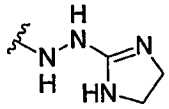
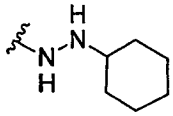
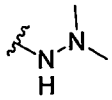
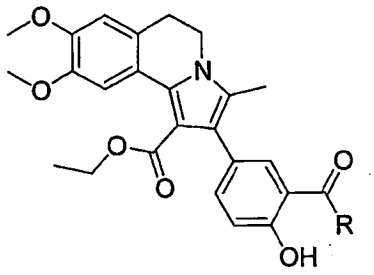
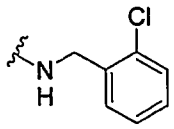
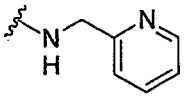
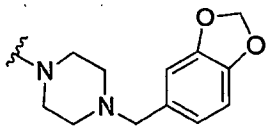
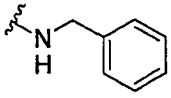
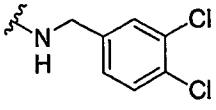
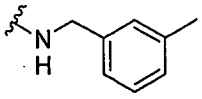
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
221		506.4	2.24	F	C
222		520.3	2.3	F	C
223		532.2	2.16	F	C
224		518.2	1.95	F	C
225		532.2	2.32	F	C
226		478.2	1.98	F	C

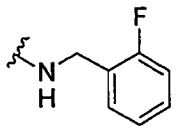
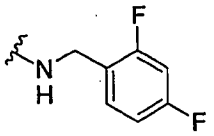
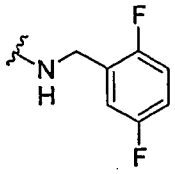
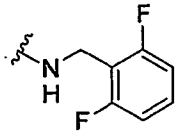
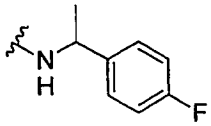
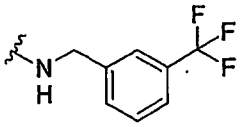
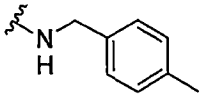
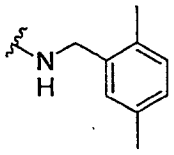
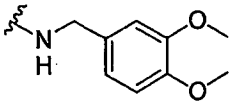
table 1

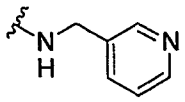
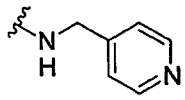
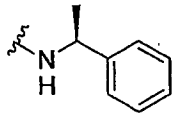
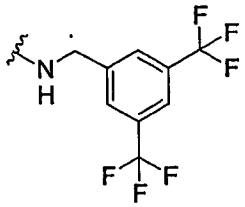
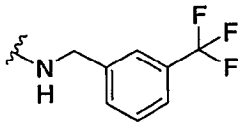
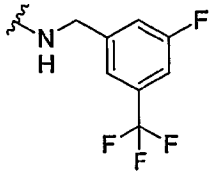
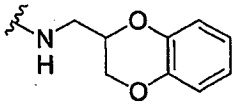
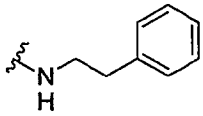
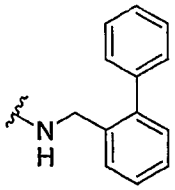
Table 2

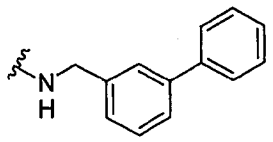
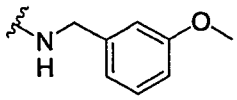
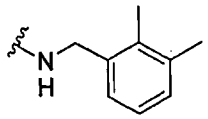
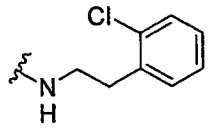
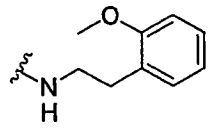
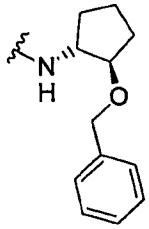
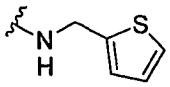
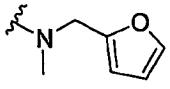
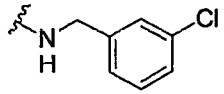
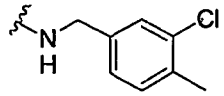
The following amides were prepared from Intermediate 2.1. using the amine coupling procedure indicated.

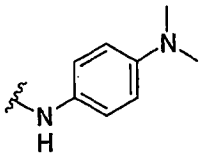
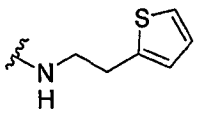
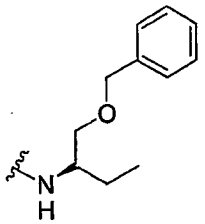
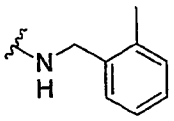
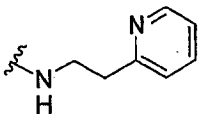
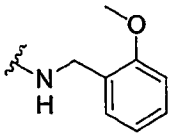
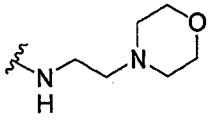
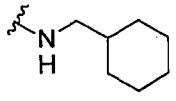
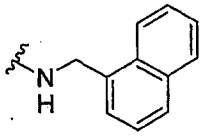


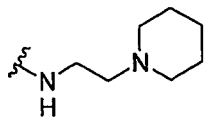
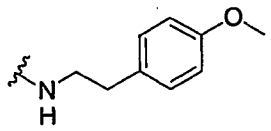
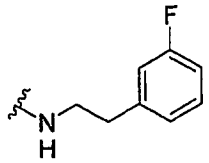
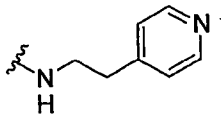
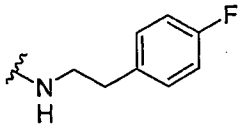
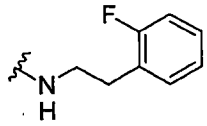
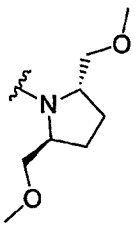
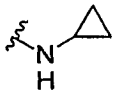
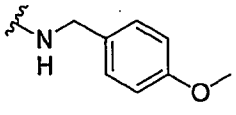
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
227		575.2	3.62	B	A
228		542.4	2.34	B	A
229		654.4	1.79	B	A
230		541.5	3.39	B	A
231		609.5	3.69	B	A
232		555.5	3.52	B	A

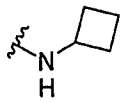
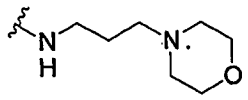
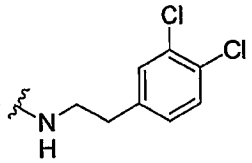
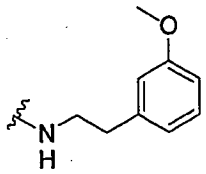
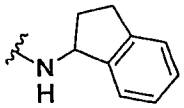
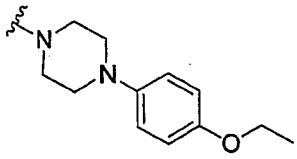
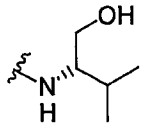
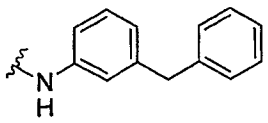
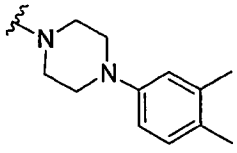
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
233		559.5	3.41	B	A
234		577.5	3.52	B	A
235		577.5	3.39	B	A
236		577.3	3.64	B	A
237		573.5	3.49	B	A
238		609.3	3.58	B	A
239		555.5	3.53	B	A
240		569.5	3.62	B	A
241		601.5	3.21	B	A

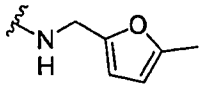
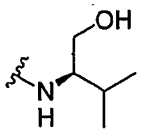
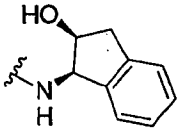
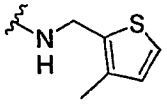
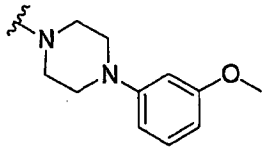
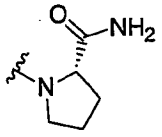
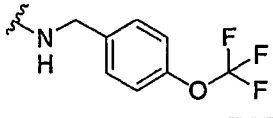
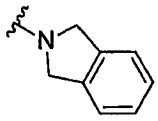
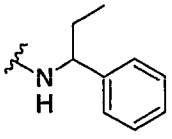
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
242		542.0	2.57	B	A
243		542.5	2.33	B	A
244		555.5	3.61	B	A
245		677.5	4.06	B	A
246		609.5	3.79	B	A
247		627.0	3.87	B	A
248		599.0	3.74	B	A
249		555.5	3.51	B	A
250		617.5	3.78	B	A

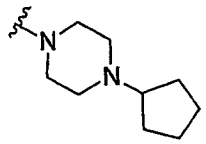
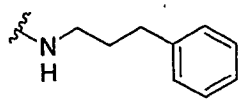
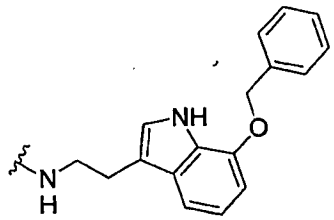
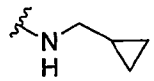
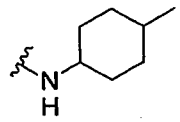
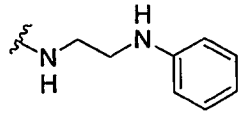
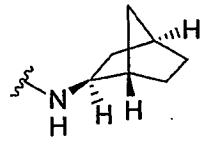
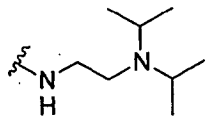
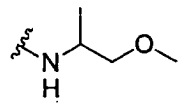
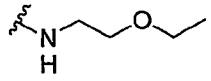
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
251		617.5	3.79	B	A
252		571.5	3.34	B	A
253		569.5	3.65	B	A
254		589.5	3.60	B	A
255		585.5	3.54	B	A
256		625.5	3.76	B	A
257		547.5	3.39	B	A
258		545.5	2.82	B	A
259		575.4	3.82	B	A
260		589.5	3.76	B	A

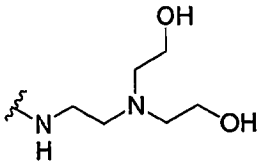
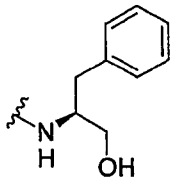
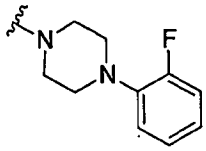
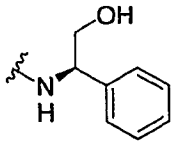
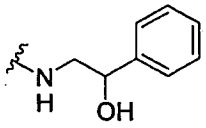
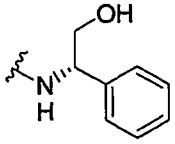
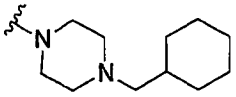
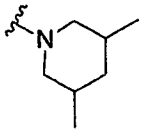
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
261		570.5	2.80	B	A
262		561.5	3.67	B	A
263		613.6	3.60	B	A
264		555.1	3.68	B	A
265		556.6	2.56	B	A
266		571.1	3.62	B	A
267		564.6	2.57	B	A
268		547.0	3.82	B	A
269		591.6	3.76	B	A

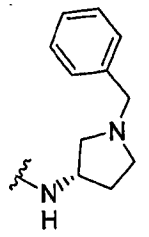
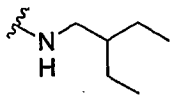
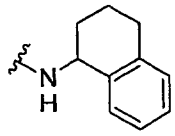
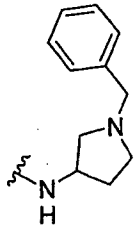
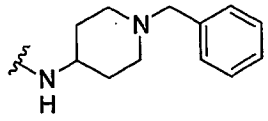
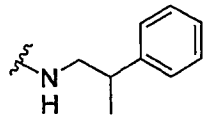
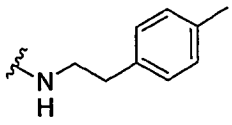
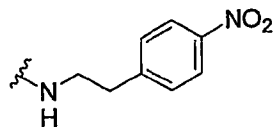
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
270		562.6	2.54	B	A
271		585.6	3.58	B	A
272		573.6	3.61	B	A
273		556.6	2.59	B	A
274		573.2	3.72	B	A
275		573.2	3.72	B	A
276		593.3	2.19	B	A
277		491.2	3.19	B	A
278		571.2	3.51	B	A

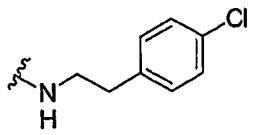
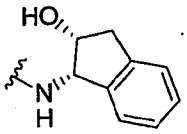
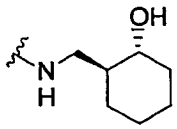
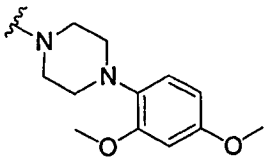
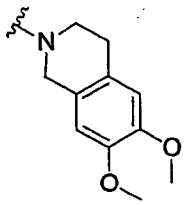
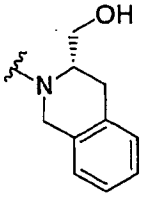
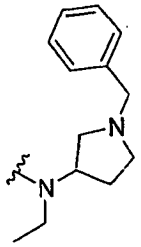
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
279		505.2	3.44	B	A
280		578.3	3.04	B	A
281		623.2	3.91	B	A
282		585.3	3.57	B	A
283		567.2	3.69	B	A
284		640.3	2.90	B	A
285		537.3	3.00	B	A
286		617.3	3.89	B	A
287		624.3	3.04	B	A

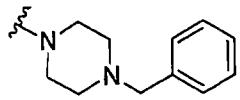
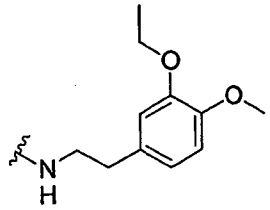
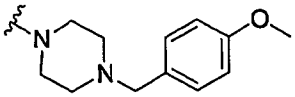
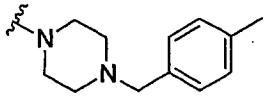
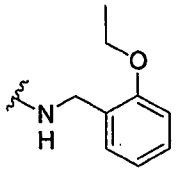
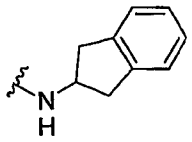
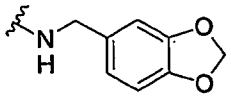
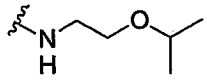
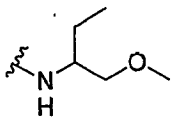
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
288		545.2	3.38	B	A
289		537.3	3.08	B	A
290		583.2	3.28	B	A
291		561.2	3.58	B	A
292		626.3	3.13	B	A
293		548.2	2.59	B	A
294		625.2	3.79	B	A
295		553.2	3.08	B	A
296		569.3	3.77	B	A

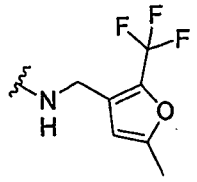
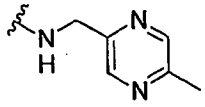
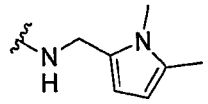
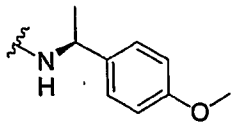
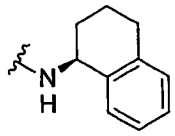
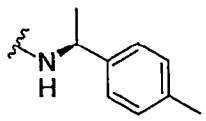
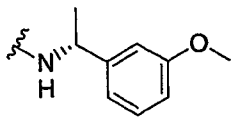
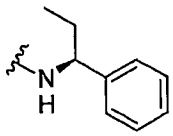
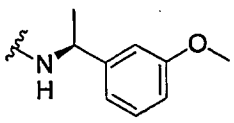
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
297		588.3	2.35	B	A
298		569.3	3.73	B	A
299		700.3	3.90	B	A
300		505.2	3.36	B	A
301		547.3	3.84	B	A
302		570.3	3.25	B	A
303		545.3	3.69	B	A
304		578.3	2.48	B	A
305		523.2	3.24	B	A
306		523.2	3.13	B	A

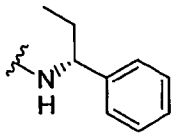
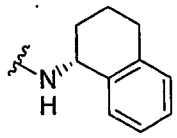
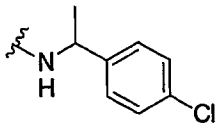
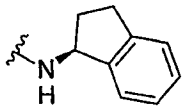
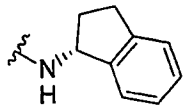
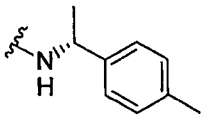
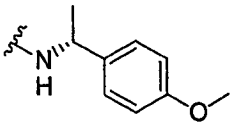
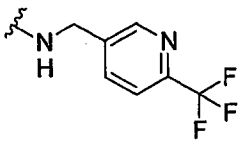
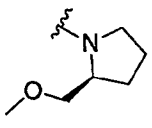
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
307		582.3	2.33	B	A
308		585.3	3.25	B	A
309		614.3	3.23	B	A
310		571.2	3.19	B	A
311		571.2	3.16	B	A
312		571.2	3.17	B	A
313		616.3	2.46	B	A
314		547.3	3.18	B	A

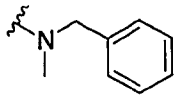
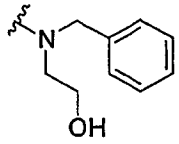
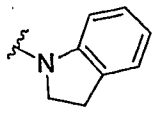
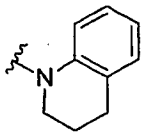
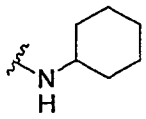
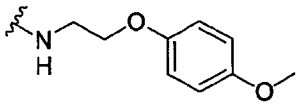
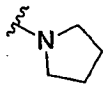
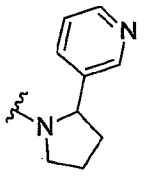
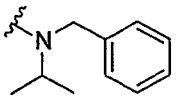
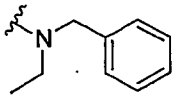
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
315		610.3	2.63	B	A
316		535.3	3.79	B	A
317		581.3	3.81	B	A
318		610.3	2.59	B	A
319		624.3	2.57	B	A
320		569.3	3.65	B	A
321		569.3	3.69	B	A
322		600.2	3.51	B	A

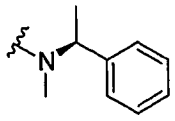
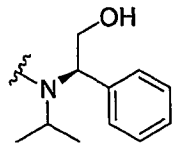
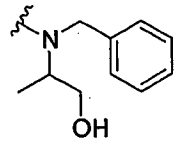
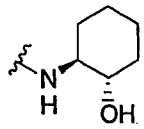
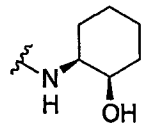
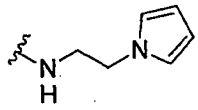
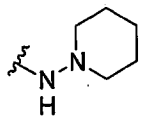
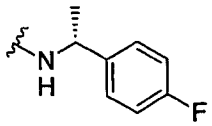
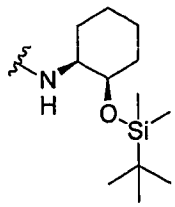
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
323		589.2	3.77	B	A
324		583.2	3.29	B	A
325		563.3	3.26	B	A
326		565.3	2.72	B	A
327		627.3	3.01	B	A
328		597.3	2.65	B	A
329		638.3	3.02	B	A

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
330		610.3	2.43	B	A
331		629.3	3.44	B	A
332		640.3	2.31	B	A
333		624.3	2.49	B	A
334		585.4	3.25	B	A
335		567.6	3.28	B	A
336		585.2	3.18	B	A
337		537.3	3.07	B	A
338		537.3	3.01	B	A

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
339		613.2	3.52	B	A
340		557.2	2.79	B	A
341		558.3	3.18	B	A
342		585.3	3.34	B	A
343		581.3	3.61	B	A
344		569.3	3.51	B	A
345		585.3	3.27	B	A
346		569.3	3.42	B	A
347		585.3	3.28	B	A

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
348		569.3	3.42	B	A
349		581.3	3.62	B	A
350		589.2	3.59	B	A
351		567.2	3.48	B	A
352		567.2	3.39	B	A
353		569.3	3.53	B	A
354		585.3	3.25	B	A
355		610.2	3.38	B	A
356		549.3	2.74	B	A

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
357		555.2	2.88	B	A
358		585.3	2.63	B	A
359		553.2	3.01	B	A
360		567.2	2.99	B	A
361		533.3	3.67	B	A
362		601.2	3.48	B	A
363		505.2	2.80	B	A
364		582.3	2.32	B	A
365		583.3	3.24	B	A
366		569.3	3.18	B	A

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
367		569.3	3.16	B	A
368		613.3	2.61	B	A
369		599.3	2.87	B	A
370		549.6	3.03	A	B
371		549.6	3.07	A	B
372		543.9	3.45	B	C
373		534.0	2.90	A	H
374		572.0	3.78	B	C
375		663.0	4.69	A	B

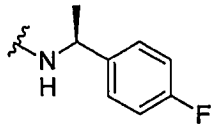
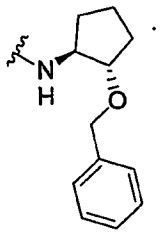
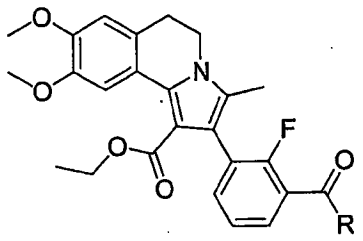
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
376		573.5	3.96	B	C
377		625.5	3.91	A	B

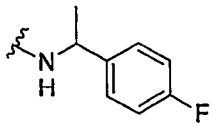
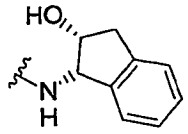
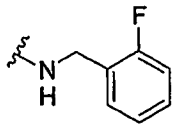
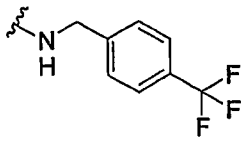
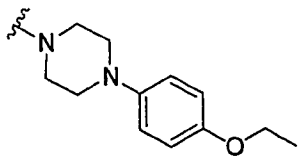
table 2

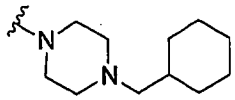
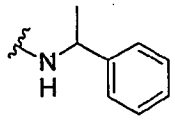
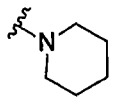
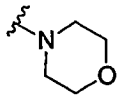
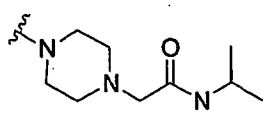
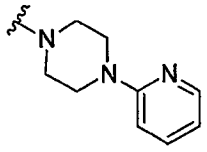
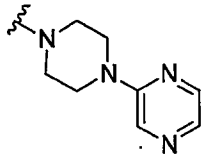
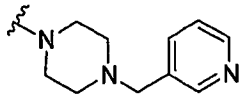
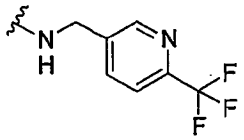
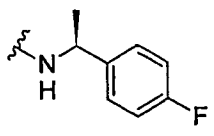
Table3

The following amides were prepared from Intermediate 3.3. using the amine coupling procedure indicated.

5



Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
378		575.2	3.40	A	F
379		585.2	3.14	A	F
380		561.2	3.31	A	F
381		611.2	3.52	A	F
382		642.2	3.22	A	F

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
383		618.1	2.61	A	F
384		556.8	3.47	A	F
385		521.2	3.85	A	F
386		522.8	3.03	A	F
387		621.0	2.43	A	F
388		599.0	3.43	A	F
389		600.0	2.96	A	F
390		613.3	2.19	A	F
391		612.1	3.31	A	F
392		575.5	3.91	B	C

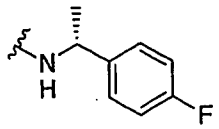
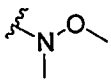
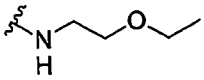
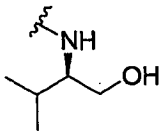
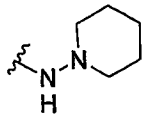
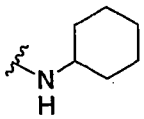
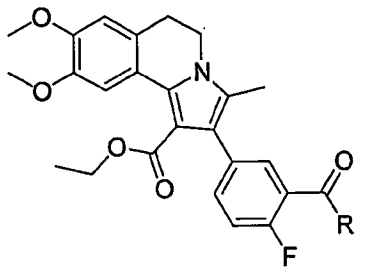
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
393		575.5	3.60	B	C
394		497.1	2.95	A	F
395		524.3	3.19	B	C
396		538.9	2.94	A	C
397		536.2	2.24	F	C
398		535.2	3.17	F	C

table 3

Table 4

The following amides were prepared from Intermediate 4.2. using the amine coupling procedure indicated.

5



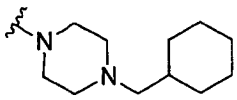
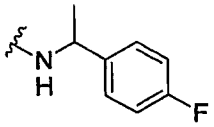
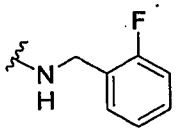
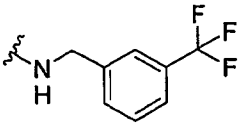
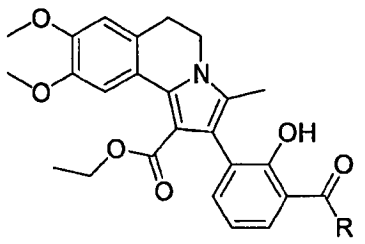
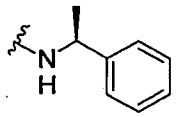
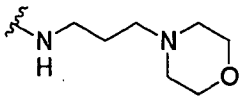
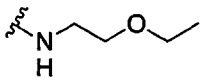
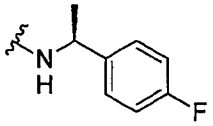
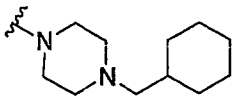
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
399		618.7	2.81	B	F
400		575.6	3.82	B	F
401		561.2	2.37	B	F
402		611.2	3.80	B	F

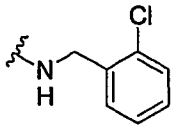
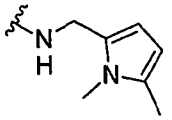
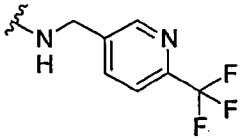
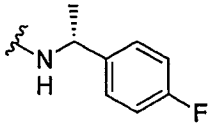
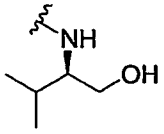
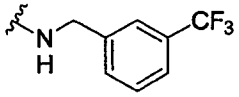
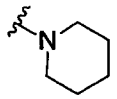
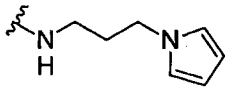
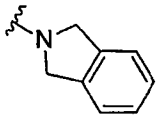
table 4

Table 5

The following amides were prepared from Intermediate 5.3. using the amine coupling procedure indicated.



Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
403		553.2	3.55	B	C
404		578.2	2.50	B	C
405		522.3	3.19	B	C
406		573.0	3.64	B	C
407		616.2	2.65	B	C

Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
408		574.3	3.63	B	C
409		557.1	3.50	B	C
410		608.9	3.45	B	C
411		572.1	3.59	B	C
412		536.3	3.20	B	C
413		608	3.38	F	C
414		473.2	2.89	F	C
415		498.2	3.01	F	C
416		589.2	3.04	F	C

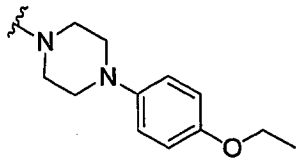
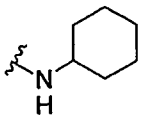
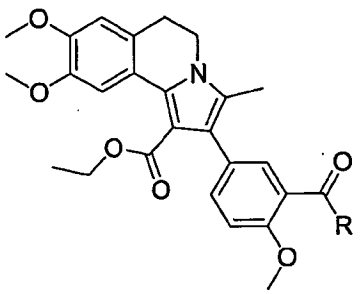
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
417		594.2	2.46	F	C
418		487.2	3.37	F	C

table 5

Table 6

The following amide was prepared from Intermediate 2.1. using the amine coupling procedure indicated, followed by methylation of the phenol using general procedure I.

5



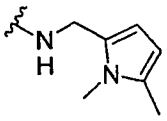
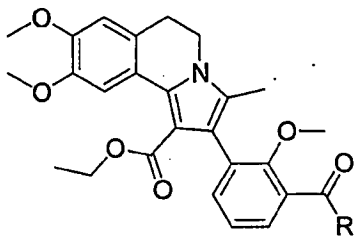
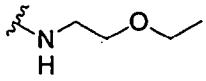
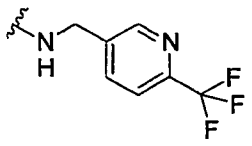
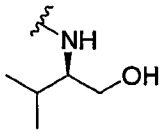
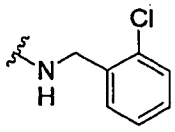
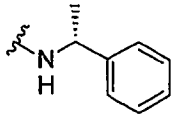
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
419		572.5	3.36	A	C

table 6

Table 7

The following amides were prepared from Intermediate 5.4. using the amine coupling procedure indicated.



Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
420		536.9	3.09	A	C
421		536.9	3.09	A	C
422		550.9	3.01	A	C
423		543.1	3.30	F	C
424		523.2	3.21	F	C

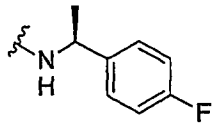
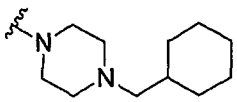
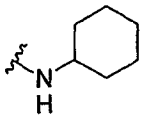
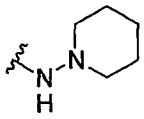
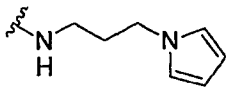
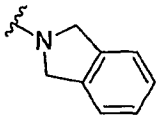
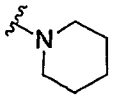
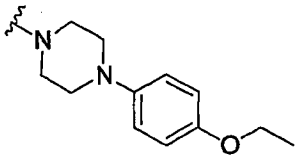
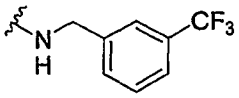
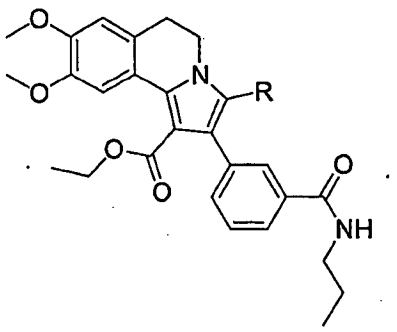
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Amine Coupling Method
425		541.1	3.23	F	C
426		630.3	2.26	F	C
427		501.2	3.25	F	C
428		548.2	2.22	F	C
429		512.2	3.70	F	C
430		521.2	3.03	F	C
431		487.17	2.90	F	C
432		654.2	2.56	F	C
433		577.1	3.38	F	C

table 7

Table 8

The following amides were prepared using general procedure J.



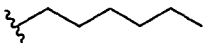
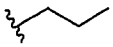
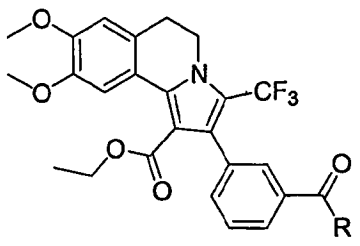
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	General Procedure
434		547	5.17	D	J
435		505	4.59	D	J

table 8

Table 9

The following amides were prepared from intermediate 6.1 using general the amine coupling procedure indicated.

5



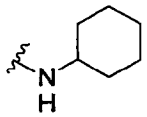
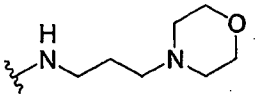
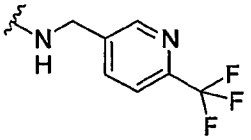
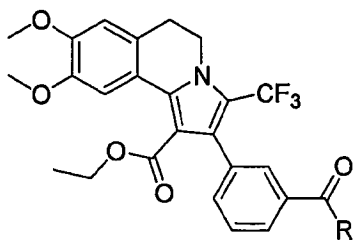
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	General Procedure
436		571.1	3.40	F	C
437		616.1	2.18	F	C
438		648.1	3.25	F	C

table 9

Table 10

The following amides were prepared from intermediates indicated, following the same procedure used for the synthesis of Intermediate 6.0.



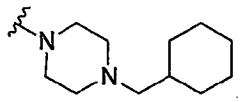
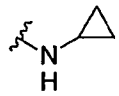
Ex.-No	R	LCMS m/z (M+1)	LCMS RT (min)	LCMS/ HPLC Method	Intemediate
439		654.2	2.51	F	7.0
440		529.1	2.93	F	8.0

table 10

Biological tests

In vitro Enzyme Inhibition Assay :

Full-length recombinant PDE 10a was expressed in Sf9 insect cells (Invitrogen, Carlsbad, California, U.S.A.) using the Bac-to-Bac™ Baculovirus Expression System (Life Technologies, Gaithersburg, MD, U.S.A.). 48 hours post infection, cells were harvested and resuspended in 20 mL (per 1L culture) Lysis Buffer (50 mM Tris-hydrochloric acid, pH 7.4, 50 mM NaCl, 1 mM $MgCl_2$, 1.5 mM EDTA, 10% glycerol plus 20 µL Protease Inhibitor Cocktail Set III [CalBiochem, La Jolla, CA, U.S.A.]). Cells were sonicated at 4°C for 1 minute and centrifuged at 10,000 RPM for 30 minutes at 4°C. Supernatant was removed and stored at -20°C for activity assays.

The test compounds were serially diluted in DMSO using two-fold dilutions to stock concentrations ranging typically from 200 µM to 1.6 µM (final concentrations in the assay range from 4 µM to 0.032 µM). 96-well assay isoplates (Wallac Inc., Atlanta, GA, U.S.A.) were loaded with 2 µL of the serially diluted individual test compounds followed by 50 µL of a dilution of crude recombinant PDE 10a-containing Sf9 cell lysate. The dilution of the lysate was selected such that less than 70% of the substrate is converted during the later incubation (typical dilution: 1:10000; dilution buffer: 50 mM Tris/hydrochloric acid pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA, 0.2% BSA). The substrate, [5',8-^{3}H] adenosine 3',5'-cyclic phosphate (1 µCi/µL; Amersham Pharmacia Biotech., Piscataway, NJ, U.S.A.), was diluted 1:2000 in assay buffer (assay buffer: 50 mM Tris/hydrochloric acid pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA) to give a final working concentration of 0.0005 µCi/µL. The enzymatic assay was initiated by addition of 50 µL (0.025 µCi) of diluted substrate. Reactions were incubated at room temperature for 60 minutes and terminated by addition of 25 µL of 18 mg/mL Yttrium Scintillation Proximity Beads (Amersham Pharmacia Biotech., Piscataway, NJ, U.S.A.). Plates were sealed and incubated at room temperature for 60 minutes. Plates were read for 30 seconds/well using a Microbeta counter (Wallac Inc., Atlanta, GA, U.S.A.). The IC_{50} values were determined by plotting compound concentration versus percent inhibition. Representative results are shown in Table 11:

Table 11

Example No.	IC_{50} (nM)
4	410
5	380
6	100
35	100
67	1600
72	150
77	220
88	370
90	410
93	140
113	< 30
116	65
158	210
165	170
170	240
175	190
227	360
234	380
244	450
267	140
284	72
286	3900
295	65
302	130
307	200
313	660
372	240

381	110
392	290
394	< 30
404	210
430	79
438	120

table 11

In vitro Proliferation Inhibition Assay:

MDA-MB-231 human breast carcinoma cells (ATCC # HTB26) were cultured in standard growth medium (DMEM), supplemented with 10% heat-inactivated FBS, 10 mM HEPES, 2 mM glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin) at 37°C in 5% CO_2 (vol/vol) in a humidified incubator. Cells were plated at a density of 3000 cells per well in 100 µL growth medium in a 96 well culture dish. 24 hours after plating, lactate dehydrogenase (LDH) activity was determined using the Cytotox 96 Non-radioactive Cytotoxicity Kit (Promega, Madison WI, U.S.A.) to yield T_{0h} LDH values. Briefly, cells were lysed with the addition of 200 µL of Lysis Buffer (included in the Promega Kit) and lysates were further diluted 1:50 in Lysis Buffer. 50 µL of diluted cell lysate were transferred to a fresh 96 well culture plate. The assay was initiated with the addition of 50 µL of substrate per well. Color development was allowed to proceed for 10-15 minutes. The assay was terminated with the addition of 50 µL of Stop Solution (included in the Promega Kit). Optical densities were determined spectrophotometrically at 490 nm in a 96 well plate reader (SpectraMax 250, Molecular Devices, Sunnyvale, CA, U.S.A.).

Test compounds were dissolved in 100% DMSO to prepare 10 mM stocks. Stocks were further diluted 1:250 in growth medium to yield working stocks of 40 µM test compound in 0.4% DMSO. Test compounds were serially diluted in growth medium containing 0.4% DMSO to maintain constant DMSO concentrations for all wells. 50 µL of fresh growth

medium and 50 μL of diluted test compound were added to each culture well to give a final volume of 200 μL. The cells with and without individual test compounds were incubated for 72 hours at which time LDH activity was measured to yield T_{72h} values. Optionally, the IC_{50} values can be determined with a least squares analysis program using compound concentration versus percent inhibition.

% Inhibition = $[1-(T_{72h\ test}-T_{0h})/(T_{72h\ ctrl}-T_{0h})] \times 100$

where

$T_{72h\ test}$ = LDH activity at 72 hours in the presence of test compound

$T_{72h\ ctrl}$ = LDH activity at 72 hours in the absence of test compound

T_{0h} = LDH activity at Time Zero

Representative results are shown in Table 12 below:

Table 12

Example No.	% inhibition at a concentration of 2 μM
4	91
5	37
6	89
8	88
35	86
67	88
72	61
77	91
88	89
90	89
93	91
113	93

Example No.	% inhibition at a concentration of 2 μM
116	57
158	90
165	84
170	91
171	89
175	90
227	89
234	90
244	91
267	52
284	90
286	84
295	89
302	89
307	32
313	88
372	87
376	87
381	92
392	88
394	89
404	90
414	37
430	87
438	82

table 12

In vivo Tumor Growth Inhibition Assay: MDA-MB-231 Tumor Xenograft Model

Inhibition of tumor growth *in vivo* is readily determined via the following assay:

MDA-MB-231 cells are cultured as described above. The cells are harvested by trypsinization, washed, counted, adjusted to $2.5x10^7$ cells/mL with ice cold phosphate-buffered saline (PBS), and subsequently stored on ice until transplantation. Xenograft experiments are conducted using eight-to-ten week-old female athymic mice with an average body mass of about 20-25 g. Approximately 5×10^6 cells in a total volume of 0.2 mL PBS are injected subcutaneously in the flank region. Thereafter the mice are randomized and divided into several groups that reflect different dosages or schedules, respectively (n = 10 mice/group). The test compounds are administered starting at day 1 at different dosages (*e.g.* 10, 20 and 40 mg/kg) and different schedules (*e.g.* Q1Dx15, Q2Dx7, Q3Dx5). Test compounds are formulated for oral administration in a vehicle for oral administration composed of polyethylene glycol-400, Cremophor®, ethanol and 0.9% saline (40:5:5:50). Tumor measurements are performed twice per week. Tumor weights are calculated using the formula $(a \times w^2)/2$, where a and w refer to the larger and smaller dimensions collected at each measurement.. Animals are sacrificed on day 15 after transplantation and plasma was harvested for pharmacokinetic analyses.

In vivo Tumor Growth Inhibition Assay: MX-1 Tumor Xenograft Model

An MX-1 breast tumor xenograft model is maintained by serial passage in NCr nu/nu female mice (Taconic Farms, Germantown, NY, USA). Tumors are aseptically harvested from mice when they weigh approximately 1g. The envelope and any non-viable areas are dissected and the viable tissue is cut into 3 x 3 x 3 mm cubes. These fragments are implanted in the axilary region of the flank of recipient mice using a trochar.

Treatment in anti-tumor efficacy studies is intiated when all mice have tumors ranging in size from 75-125 mg. There are typically 10 mice in each experimental group. Each

experiment contains an untreated control group to monitor tumor growth kinetics, a vehicle-treated control group, and a positive agent control group to assess the response of the model in each experiment to an agent with an expected degree of anti-tumor efficacy. Lack of conformance of any of the controls to the historical ranges for the model constitutes a reason to nullify the study. The test compounds were administered starting at different dosages (e.g. 75 and 150 mg/kg) and different schedules (e.g. q1d x 10, bid x 10). Test compounds are formulated for oral administration once per day in a vehicle composed of 51% PEG400/ 12% ethanol/ 12% Cremophor® EL/ 0.1 N hydrochloric acid . Tumor size is recorded in whole mm as measured in two perpendicular dimensions. Animal body weights are recorded in tenths of grams. Both measurements are collected two to three times per week. Animals are sacrificed on day 10 after the last dose and last measurements.

Tumor weights are calculated using the equation $(l \times w^2)/2$, where l and w refer to the larger and smaller dimensions collected at each measurement. Efficacy is measured as the percent suppression of tumor growth expressed as $\%\Delta T/\Delta C$, where ΔT and ΔC represent the change in the size of the average tumor in the treated and control groups, respectively, over the treatment period. Significance is evaluated using a Student's t-test with a $p<0.05$.

B. Operative examples relating to pharmaceutical compositions

The compounds according to the invention can be converted into pharmaceutical preparations as follows:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg, diameter 8 mm, curvature radius 12 mm.

Preparation:

The mixture of active component, lactose and starch is granulated with a 5% solution (m/m) of the PVP in water. After drying, the granules are mixed with magnesium stearate for 5 min. This mixture is moulded using a customary tablet press (tablet format, see above). The moulding force applied is typically 15 kN.

Orally administrable suspension:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

A single dose of 100 mg of the compound according to the invention is provided by 10 ml of oral suspension.

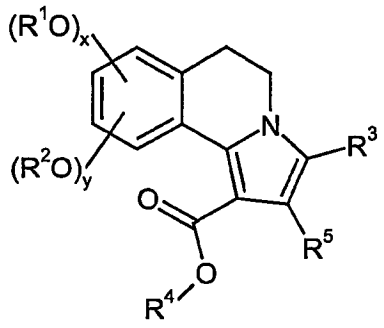
Preparation:

The Rhodigel is suspended in ethanol and the active component is added to the suspension. The water is added with stirring. Stirring is continued for about 6h until the swelling of the Rhodigel is complete.

Claims

We claim:

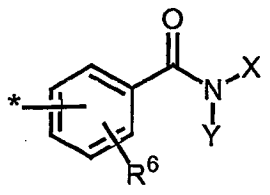
1. A compound of the formula



(I)

wherein

x and y		independently from each other denote zero or 1;
R^1 and R^2		independently from each other denote hydrogen, C_{1-4}-alkyl or trifluoromethyl or
R^1 and R^2		together form a C_{1-4}-alkylene bridge;
R^3 and R^4		independently from each other denote C_{1-6}-alkyl optionally further substituted with halogen up to perhalo;
R^5		denotes a radical of the formula



wherein

R^6 denotes C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, halogen, hydrogen, hydroxy or C_{1-6}-alkoxy;

X and Y independently from each other denote

i) hydrogen;

ii) C_{1-6}-alkoxy;

iii) C_{3-8}-cycloalkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, benzyloxy, C_{1-6}-trialkylsilyloxy, halogen and C_{1-6}-alkoxy;

iv) C_{5-8}-cycloalkyl fused to C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of hydoxyl, C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, C_{3-8}-cycloalkyl, halogen and C_{1-6}-alkoxy;

v) C_5-C_{10}-bridged bicycloalkyl;

vi) C_6-C_{10}-aryl optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkoxy, (C_{1-6}-alkyl)-carbonyl, (C_{1-6}-alkoxy)-carbonyl, trifluoromethyl, trifluoromethoxy and halogen;

vii) phenyl fused to a 5- to 7-membered saturated cycloalkyl, optionally containing up to two hetero atoms selected from the group consisting of O, N, and S;

viii) heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkoxy, phenyloxy, benzyloxy, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, halogen and benzyl;

ix) heteroaryl; or

x) C_{1-6}-alkyl, optionally having from 1 to 3 substituents selected from the group consisting of

a) halogen up to perhalo,

b) cyano,

c) $-OR^7$,

d) $-NR^7R^8$,

e) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, nitro, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, $-OR^7$, $-NR^7R^8$, (C_{1-6}-alkyl)-carbonyl, (C_{1-6}-alkoxy)-carbonyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, $-C(O)NR^7R^8$, cyano, $-SR^7$, and C_6-C_{10}-aryl,

f) phenyl fused to a 5- to 7-membered saturated cycloalkyl, optionally containing up to two hetero atoms selected from the group consisting of O, N, and S,

g) heteroaryl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{3-8}-cycloalkyl, hydroxy, C_{1-6}-alkoxy, benzyloxy, halogen and trifluoromethyl,

h) heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, halogen and benzyl, and

i) C_{3-8}-cycloalkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy and hydroxy;

wherein R^7 and R^8 independently from each other denote

1) hydrogen,

2) C_{1-6}-alkyl, optionally further substituted with 1 to 3 substituents selected from the group consisting of hydroxyl and halogen,

3) C_{3-8}-cycloalkyl,

4) benzyl,

5) C_6-C_{10}-aryl optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkoxy, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy and halogen, or

6) heteroaryl;

or

X and Y together with the nitrogen atom to which they are attached form heteroaryl or heterocyclyl, wherein said heteroaryl or heterocyclyl may optionally have from 1 to 3 substituents selected from the group consisting of

i) C_{3-8}-cycloalkyl;

ii) C_{1-6}-alkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{3-8}-cycloalkyl, hydroxy, C_{1-6}-alkoxy, halogen, phenylamino, morpholinyl, (C_{1-6}-alkyl)-aminocarbonyl, benzo[2,3]dioxolyl and C_6-C_{10}-aryl, wherein said aryl is optionally substituted with C_{1-6}-alkyl or C_{1-6}-alkoxy;

iii) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkoxy, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy and cyano,

iv) hydroxy;

v) C_{1-6}-alkoxy;

vi) C_{1-6}-dialkylamino;

vii) (C_{1-6}-alkoxy)-carbonyl;

viii) aminocarbonyl; and

ix) heteroaryl;

or

X and Y together with the nitrogen atom to which they are attached form heterocyclyl fused to C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkoxy and hydroxymethyl;

or

X denotes hydrogen and

Y denotes $-NR^9R^{10}$;

wherein R^9 and R^{10} independently from each other denote

1) hydrogen,
2) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-6}-alkoxy, trifluoromethoxy and trifluoromethyl,
3) heterocyclyl,
4) C_{3-8}-cycloalkyl, or
5) C_{1-6}-alkyl;

or

R^9 and R^{10} together with the nitrogen atom to which they are attached form heterocyclyl or heteroaryl, wherein said heteroaryl or heterocyclyl may optionally have from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen and methoxymethyl;

and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

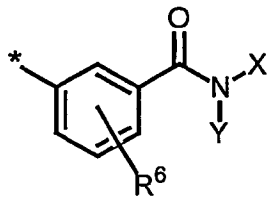
2. A compound as recited in claim 1, wherein

x and y independently from each other denote zero or 1;

R^1 and R^2 independently from each other denote hydrogen, C_{1-4}-alkyl or trifluoromethyl;

R^3 and R^4 independently from each other denote C_{1-6}-alkyl optionally further substituted with halogen up to perhalo;

R^5 denotes a radical of the formula



wherein

R^6 denotes halogen, hydrogen, hydroxy or C_{1-6}-alkoxy;

X and Y independently from each other denote

i) hydrogen;

ii) C_{1-6}-alkoxy;

iii) C_{3-8}-cycloalkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, benzyloxy and C_{1-6}-trialkylsilyloxy;

iv) C_{5-8}-cycloalkyl fused to C_6-C_{10}-aryl, optionally substituted with 1 to 3 hydoxyl;

v) C_5-C_{10} bridged bicycloalkyl;

vi) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy and (C_{1-6}-alkyl)-carbonyl;

vii) phenyl fused to a 5- to 7-membered saturated cycloalkyl, optionally containing up to two hetero atoms selected from the group consisting of O, N, and S;

viii) heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkoxy, phenyloxy, benzyloxy, and benzyl;

ix) heteroaryl; or

x) C_{1-6}-alkyl, optionally having from 1 to 3 substituents selected from the group consisting of

a) halogen up to perhalo,

b) cyano,

c) $-OR^7$,

d) $-NR^7R^8$,

e) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, nitro, hydroxy, C_{1-6}-alkyl, $-NR^7R^8$, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy and C_6-C_{10}-aryl,

f) phenyl fused to a 5- to 7-membered saturated cycloalkyl, optionally containing up to two hetero atoms selected from the group consisting of O, N, and S,

g) heteroaryl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, benzyloxy and trifluoromethyl,

h) heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl and benzyl, and

i) C_{3-8}-cycloalkyl, optionally further substituted with 1 to 3 substituents hydroxy;

wherein R^7 and R^8 independently from each other denote

1) hydrogen,
2) C_{1-6}-alkyl, optionally further substituted with 1 to 3 substituents hydroxyl,
3) benzyl,
4) C_6-C_{10}-aryl, optionally further substituted with 1 to 3 substituents C_{1-6}-alkoxy, or
5) heteroaryl;

or

X and Y together with the nitrogen atom to which they are attached form heteroaryl or heterocyclyl, optionally having from 1 to 3 substituents selected from the group consisting of

i) C_{3-8}-cycloalkyl;
ii) C_{1-6}-alkyl, optionally having from 1 to 3 substituents selected from the group consisting of C_{3-8}-cycloalkyl, hydroxy, C_{1-6}-alkoxy, phenylamino, morpholinyl, (C_{1-6}-alkyl)-aminocarbonyl, benzo[2,3]dioxolyl and C_6-C_{10}-aryl, wherein said aryl is optionally substituted with C_{1-6}-alkyl or C_{1-6}-alkoxy;
iii) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkoxy, trifluoromethyl and cyano;
iv) hydroxy;
v) C_{1-6}-alkoxy;
vi) C_{1-6}-dialkylamino;
vii) (C_{1-6}-alkoxy)-carbonyl;
viii) aminocarbonyl; and
ix) heteroaryl;

or

X and Y together with the nitrogen atom to which they are attached form heterocyclyl fused to C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy and hydroxymethyl;

or

X denotes hydrogen and

Y denotes $-NR^9R^{10}$;

wherein R^9 and R^{10} independently from each other denote

1) hydrogen,
2) C_6-C_{10}-aryl, optionally having from 1 to 3 substituents selected from the group consisting of halogen, C_{1-6}-alkyl and trifluoromethyl,
3) heterocyclyl,
4) C_{3-8}-cycloalkyl, or
5) C_{1-6}-alkyl;

or

R^9 and R^{10} together with the nitrogen atom to which they are attached form heterocyclyl or heteroaryl, wherein said heterocyclyl or heteroaryl optionally have from 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl and methoxymethyl;

and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

3. A compound as recited in claim 1, wherein

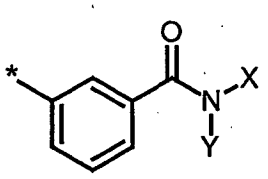
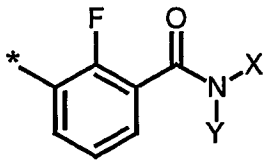
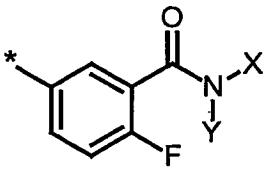
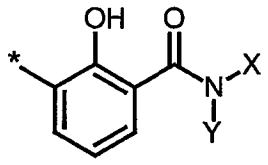
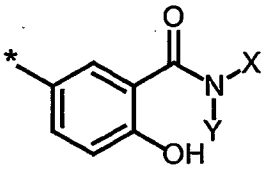
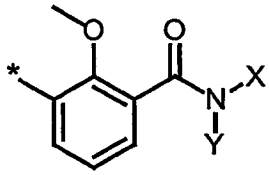
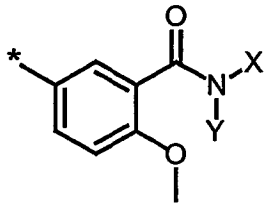
x and y each other denote 1

R^1 and R^2 independently from each other denote hydrogen or C_{1-4}-alkyl;

R^3 denotes C_{1-6}-alkyl or trifluoromethyl;

R^4 denotes C_{1-4}-alkyl;

R^5 denotes a radical of the formula selected from the group consisting of:


,

,

,

,

,

,
and

;

wherein

X and Y independently from each other denote

i) hydrogen;

ii) C_{1-6}-alkoxy;

iii) C_{3-8}-cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, said C_{3-8}-cycloalkyl

optionally having from 1 to 2 substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, benzyloxy and *tert*-butyldimethylsilyloxy;

iv) indanyl, 2-hydroxyindanyl, or 1,2,3,4-tetrahydronaphthalenyl;

v) [2.2.1]bicycloheptane;

vi) naphthyl, 4-methoxyphenyl, 3-(C_{1-6}-alkoxycarbonyl)phenyl or 2-methoxy-4-methylphenyl;

vii) benzo[2,3]dioxolyl;

viii) pyrrolidinyl, optionally having from 1 to 2 substituents selected from the group consisting of C_{1-6}-alkoxy, phenyloxy, benzyloxy and benzyl;

ix) thiazolyl, or pyridyl; or

x) C_{1-6}-alkyl, optionally having from 1 to 2 substituents selected from the group consisting of

a) halogen up to perhalo,

b) cyano,

c) hydroxy, C_{1-6}-alkoxy, benzyloxy, hydroxy-C_{2-6}-alkoxy, or methoxyphenoxy,

d) C_{1-6}-dialkylamino, di-(hydroxy-C_{1-6}-alkyl)-amino, pyridylamino, or anilino,

e) C_{6-10}-aryl selected from the group consisting of naphthyl and phenyl, said C_{6-10}-aryl optionally having from 1 to 2 substituents selected from the group consisting of fluoro, chloro, bromo, iodo, nitro, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, phenyl, amino and C_{1-6}-dialkylamino,

f) benzo[2,3]dioxolyl, or 2,3-dihydrobenzo[1,4]dioxinyl,

g) heterocyclyl selected from the group consisting of pyrazolyl, pyrazinyl, pyrrolyl, furyl, indolyl, thienyl, imidazoyl, and pyridyl, said heterocyclyl optionally having from 1 to 2

substituents selected from the group consisting of C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, benzyloxy and trifluoromethyl,

h) morpholino, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, optionally further substituted with 1 to 2 substituents C_{1-6}-alkyl or benzyl, and

i) C_{3-8}-cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, said C_{3-8}-cycloalkyl optionally being further substituted with 1 to 2 substituents hydroxy;

or

X and Y together with the nitrogen atom to which they are attached form

i) morpholino, optionally further subsituted with 1 to 2 substituents C_{1-6}-alkyl;

ii) piperidinyl, optionally having from 1 to 2 substituents selected from the group consisting of hydroxyl, hydroxymethyl and C_{1-6}-alkyl;

iii) pyrrolidinyl, optionally having from 1 to 2 substituents selected from the group consisting of C_{1-6}-dialkylamino, pyridyl, carboxamido, C_{1-6}-alkoxy, phenylaminomethyl, methoxymethyl and methoxyphenyl; or

iv) piperazinyl, optionally having from 1 to 2 substituents selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, benzyl, morpholinoethyl, C_{1-6}-alkyl, (C_{1-6}-alkoxy)-carbonyl, (C_{1-6}-alkylaminocarbonyl)methyl, pyridyl, pyrazinyl, pyridylmethyl, benzo[2,3]dioxolyl and phenyl, wherein said phenyl is optionally substituted with 1 to 2 substituents selected from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, cyano and C_{1-6}-alkoxy;

or

X and Y together with the nitrogen atom to which they are attached form dimethoxytetrahydroisoquinolinyl, 2-methyl-6-fluorotetrahydroquinolinyl, indolinyl, isoindolinyl or 2-hydroxymethyltetrahydroisoquinolinyl;

or

X denotes hydrogen and

Y denotes

a) phenylamino, having from 1 to 2 substituents selected from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl and C_{1-6}-alkyl;

b) piperidinyl, optionally further substituted with 1 to 2 C_{1-6}-alkyl;

c) triazolyl;

d) pyrrolidinyl, optionally further substituted with 1 to 2 methoxymethyl;

e) morpholino;

f) imidazoyl;

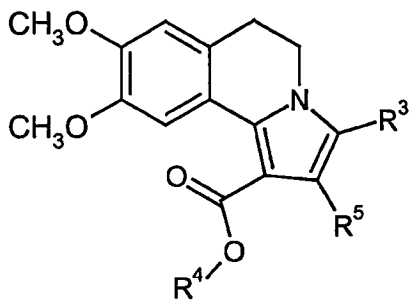
g) C_{3-8}-cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

h) C_{1-6}-dialkylamino; or

i) azepanyl;

and an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

4. A compound as recited in claim 1, wherein the compound has the formula (I'):

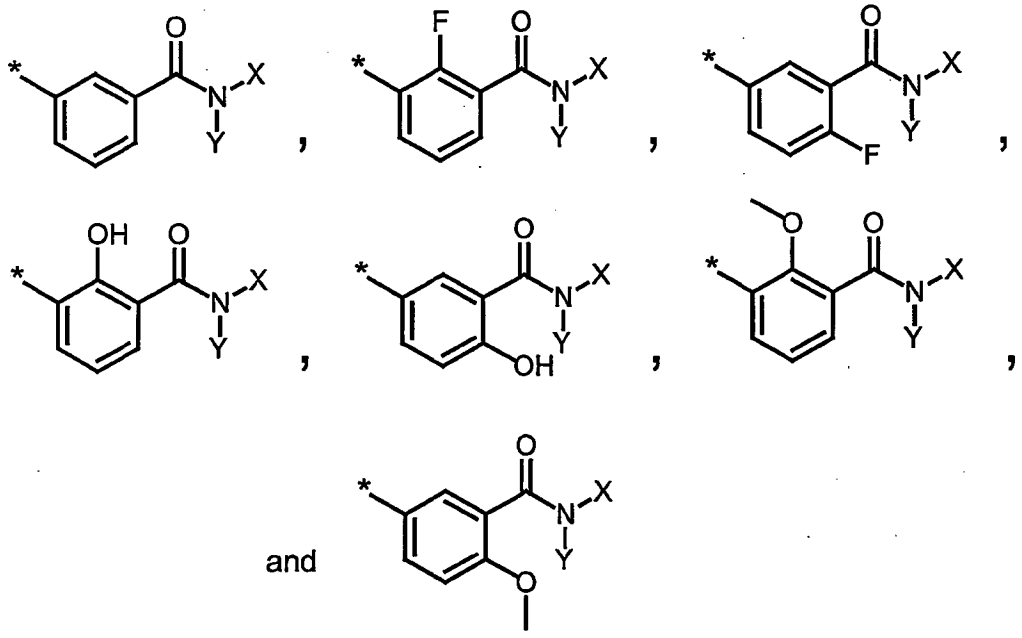


(I')

wherein R^3 to R^5 are defined as described in claim 1.

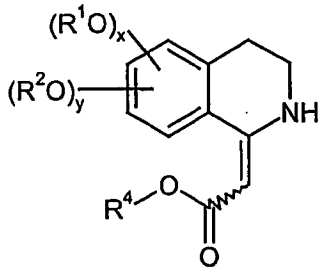
5. A compound as recited in claim 1, wherein

R^5 denotes a radical of the formula selected from the group consisting of:



and

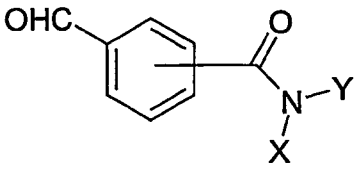
6. A process for manufacturing a compound of claim 1, comprising the reaction of a compound of the formula



(IV)

wherein x, y, R^1, R^2 and R^4 are as defined in claim 1,

[A] with the compounds of the formulae

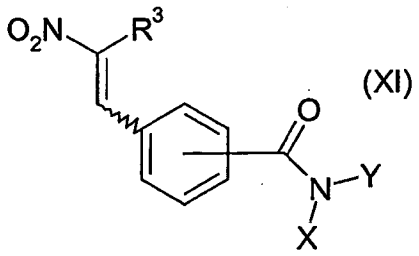


(III)

and R^3-CH_2-NO_2 (III)

wherein R^3 and R^5 are as defined in claim 1, or

[B] with a compound of the formula



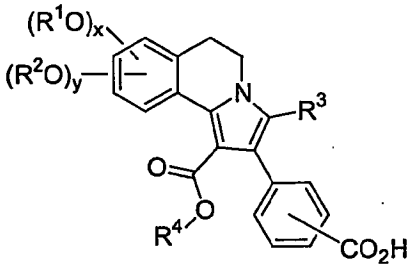
(XI)

wherein R^3 and R^5 are as defined in claim 1,

and optionally

[C] conversion of the compound obtained through either process [A] or [B] into an isomer, a pharmaceutically acceptable salt, a hydrate, or a hydrate of a pharmaceutically acceptable salt thereof.

7. A process for manufacturing a compound of claim 1, comprising the reaction of a compound of the formula



V

wherein X, Y, R^1, R^2 and R^4 are as defined in claim 1,

with a compound of formula HNXY.

8. A compound according to claim 1 for the treatment and/or prophylaxis of disorders.

9. A medicament containing at least one compound according claim 1 in combination with at least one pharmaceutically acceptable, pharmaceutically safe carrier or excipient.

10. The use of a compound according to claim 1 for manufacturing a medicament for the treatment and/or prophylaxis of cancer.

11. The medicament according to Claim 9 for the treatment and/or prophylaxis of cancer.

12. The process for controlling cancer in humans and animals by administration of an therapeutically effective amount of at least one compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/40328

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANDERSON W K ET AL: "SYNTHESIS AND ANTILEUKEMIC ACTIVITY OF BIS(CARBAMOYL)OXYMETHYL-SUBSTI TUTED PYRROLO2,1-AISOQUINOLINES, PYRROLO1,2-AQUINOLINES, PYRROLO2,1-AISOBENZAZEPINES, AND PYRROLO1,2-ABENZAZEPINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 31, no. 11, 1988, pages 2097-2102, XP001068970 ISSN: 0022-2623 compounds 1-3 abstract --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2003	21/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ɔnal Application No
PCT/US 02/40328

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 48144 A (ERGUEDEN JENS-KERIM ;FLUBACHER DIETMAR (DE); NIEWOEHNER ULRICH (DE) 20 June 2002 (2002-06-20) page 1, line 4 - line 6; claim 1	1-12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In nal Application No
PCT/US 02/40328

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0248144 A	20-06-2002	AU 2798502 A	24-06-2002
		WO 0248144 A1	20-06-2002

Form PCT/ISA/210 (patent family annex) (July 1992)